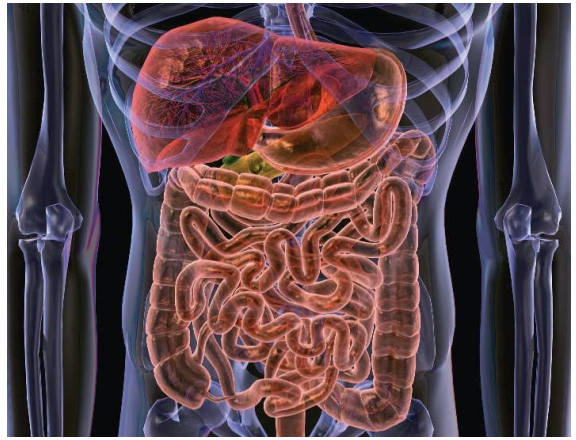
THE HUMAN MICROBIOME: THE ROLE OF OUR SECOND GENOME IN HEALTH AND DISEASE

James R. Brown

Computational Biology, Target Sciences

10/18/2018

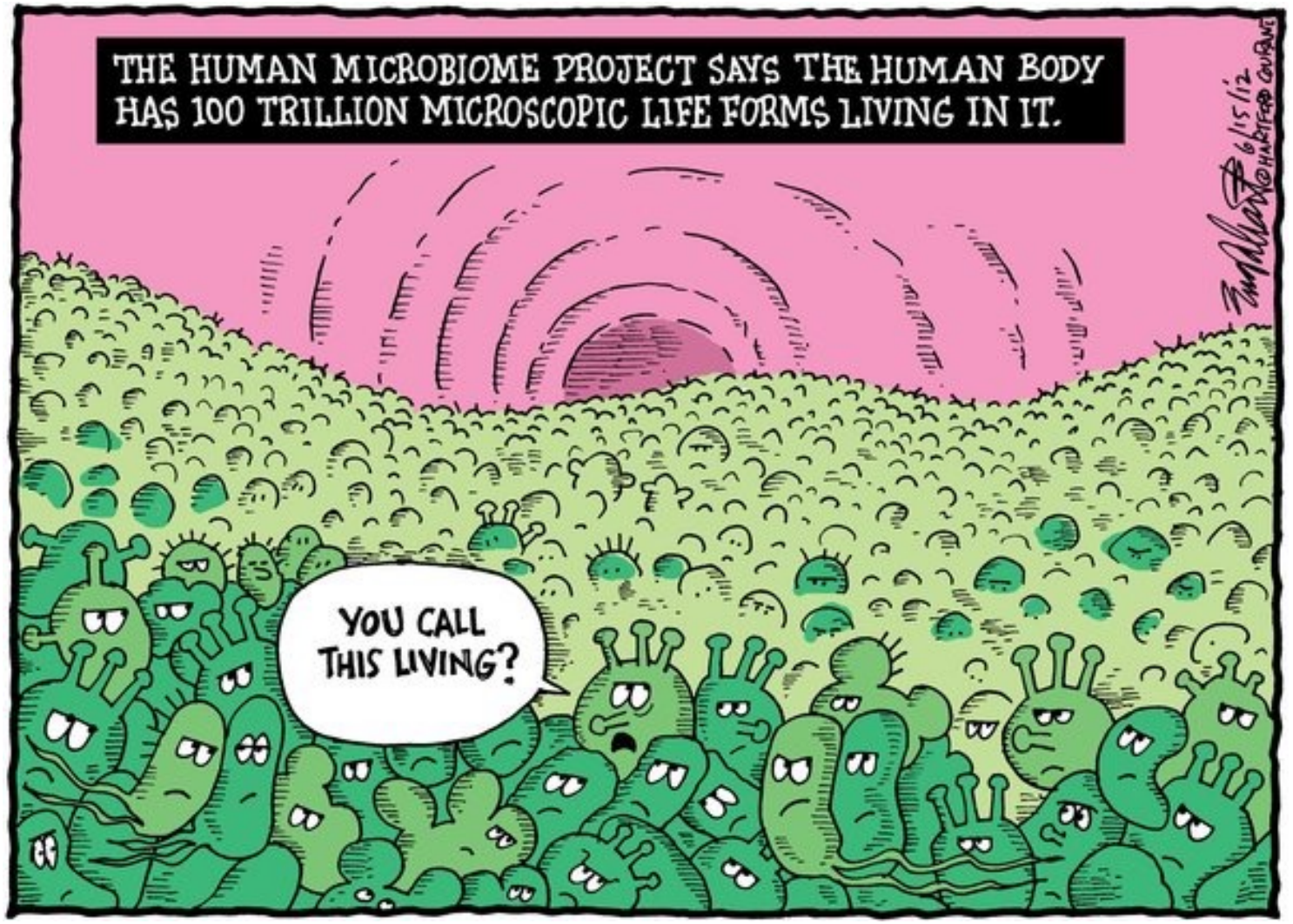


Outline

1. **Microbiome – why now?**
2. The microbiome, immunity and inflammation
3. GSK Pharma R&D microbiome activities

The Microbiome and Human Health

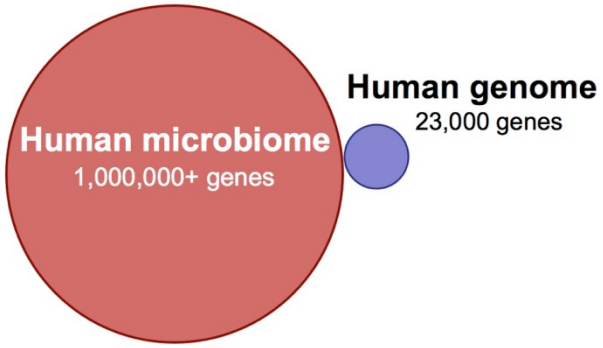
Our Friends and, at times, Foes

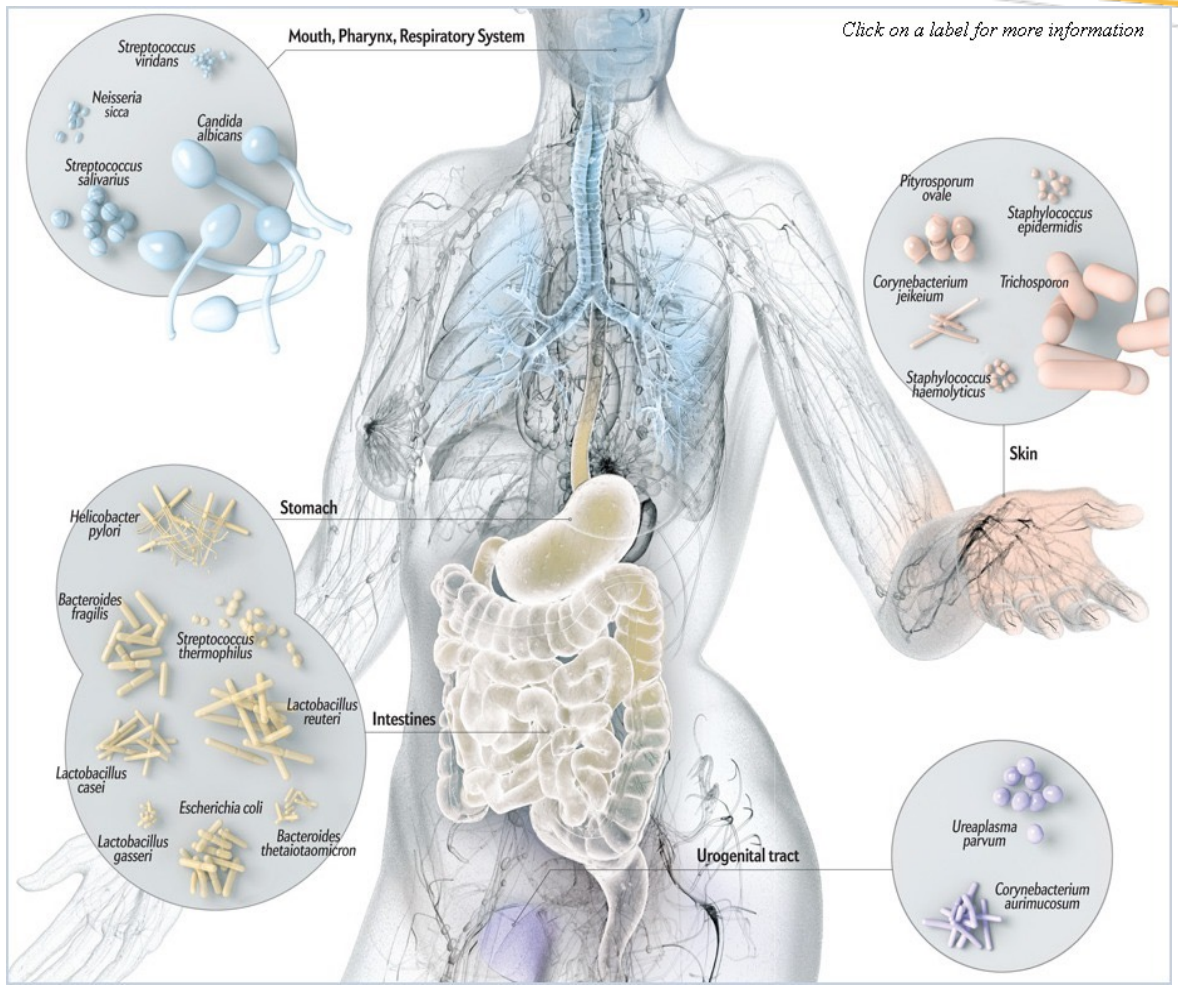


We Are Not Alone…

The human-microbial ecosystem

- **Microbiota** –10^{14} bacteria in the gut
  - 10 times more gut bacteria than human cells
  - > 1,000 species
- **Microbiome** – 100 times more bacterial genes than in human genome



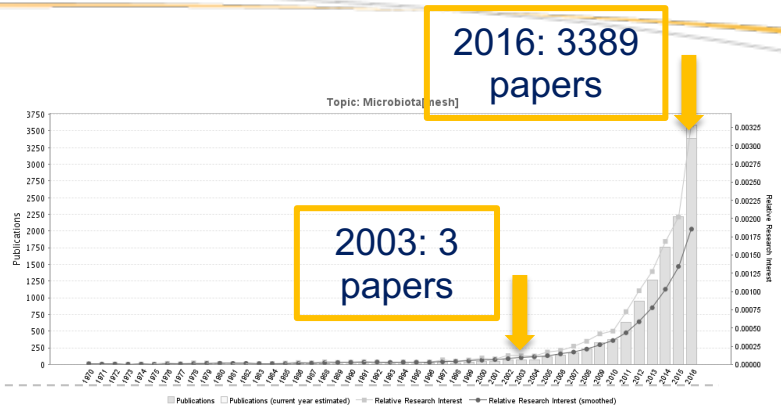


Expansive Growth of Microbiome Science

Potential for innovative medicines, consumer health products and vaccines

Exponential growth in science

- New science linking microbiome with disease occurrence and possible causality



R&D investment expanding

- Large public funding initiatives
- Increasing investment activity by pharma, biotech, VCs and food industry
- Most microbiome biotechs early phase but clinical studies increasing

Rise in public interest

- High consumer interest in microbiome oriented pharma health products
- Global market for microbiome therapeutics projected to be > $3 billion by 2024 (http://www.transparencymarketresearch.com/human-microbiome-market.html)

μBiome american gut

Int'l & US open source, public microbiomes

The New York Times

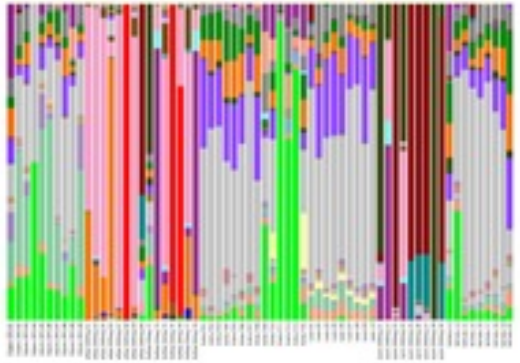
BBC

Microbiome DNA Sequencing Strategies

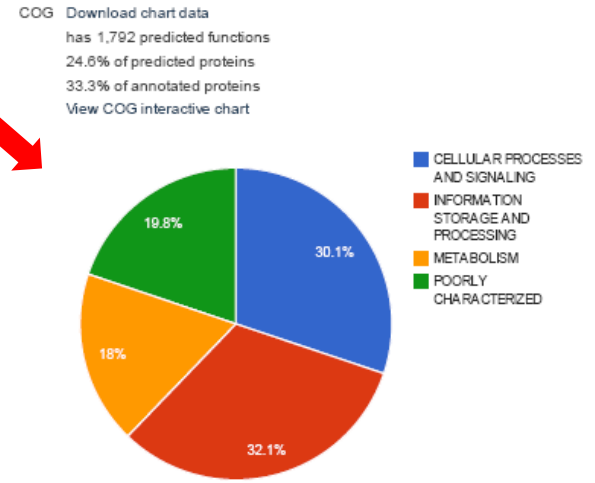
Next Generation DNA Sequencing (NGS) reveals difficult to culture microbial ecosystems

- Sample prep – common initial step
  - Total genomic DNA isolated from feces, skin, lung sputum, etc
- 16s rRNA amplicon sequencing – who's there?
  - Over 2.3 million known bacterial 16s rRNAs
  - Targeted DNA sequencing – species barcode
  - Provides species and abundances
  - *18s ITS rRNA used for fungal or mycobiome*
- Metagenomic sequencing – what they do?
  - Determine pan-genome content (bacterial, fungal & viral)
- Metagenomic transcriptomics – what is active?
  - Convert RNA into cDNA then sequence
- Challenge – computational analysis of terabytes of data making biological interpretation very complex

Ilumina MiSeq DNA Sequencer



Relative cluster sizes are reflect relative abundance in initial sample and microbiome is rendered as a species breakdown chart



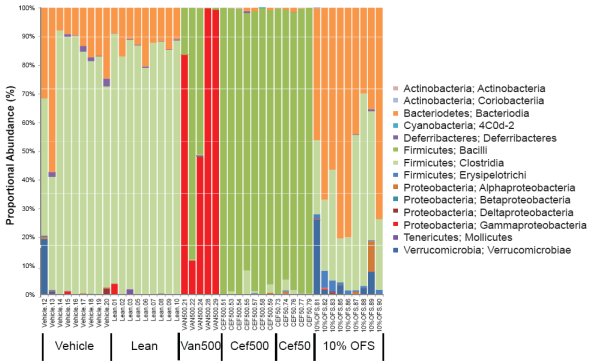
Overview of Microbiome Analysis Techniques

16S rRNA data analysis – What we can do with the data

Metrics to summarize and compare microbiome samples:

Relative abundance

- Proportional (not absolute) abundance of a given bacterial taxonomic classification.



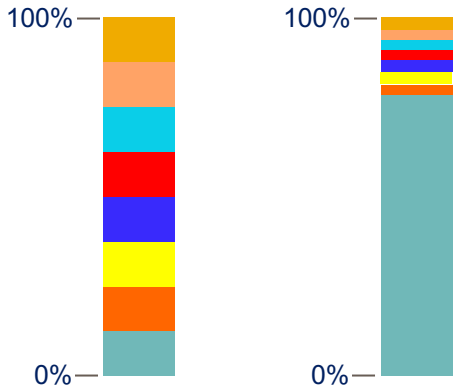
Phylum-level (broad)

…

Genus/species-level (specific)

Alpha Diversity

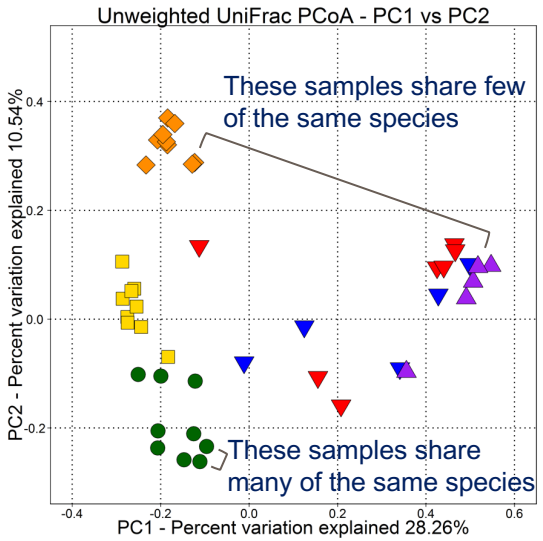
- Richness or entropy of the bacteria within a single sample. Usually Shannon's entropy (H)



High Entropy Low Entropy

Beta Diversity

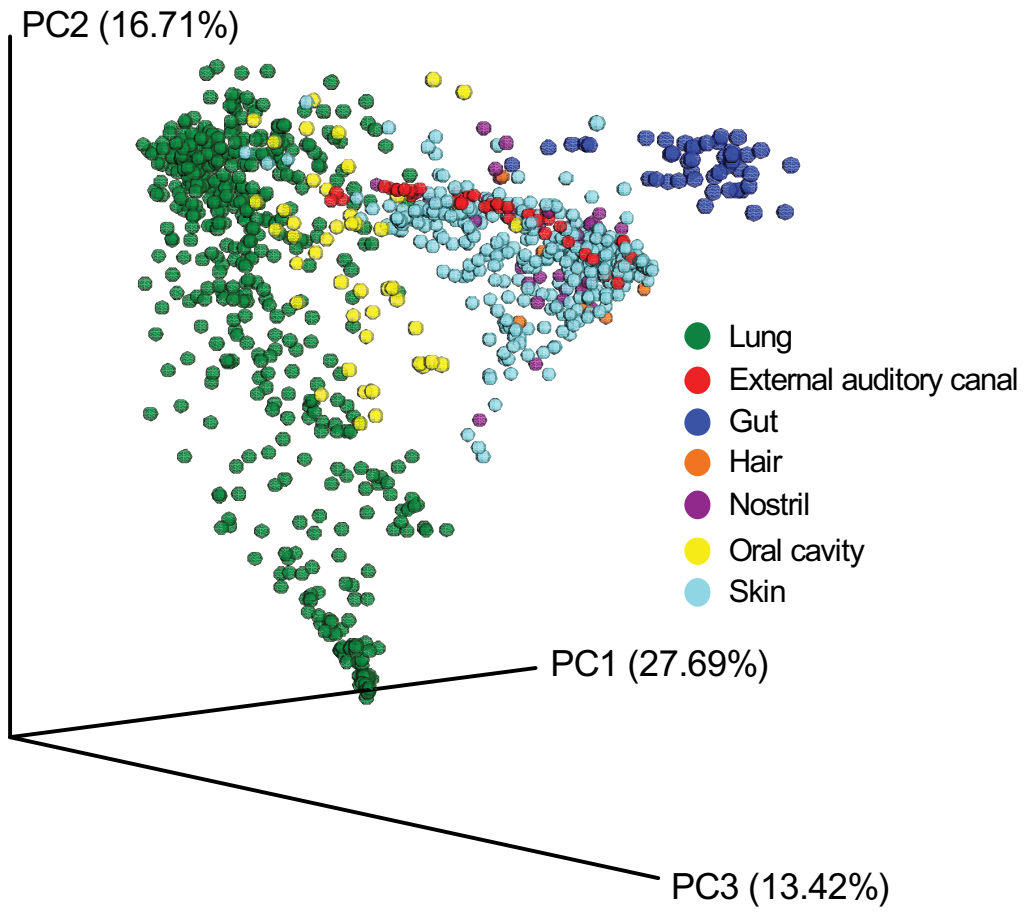
- Similarity of overall bacterial content between samples



Slide courtesy of David Mayhew, CB, GSK

“Healthy” Microbiome Variation – Body Site

Microbiome composition varies by body site

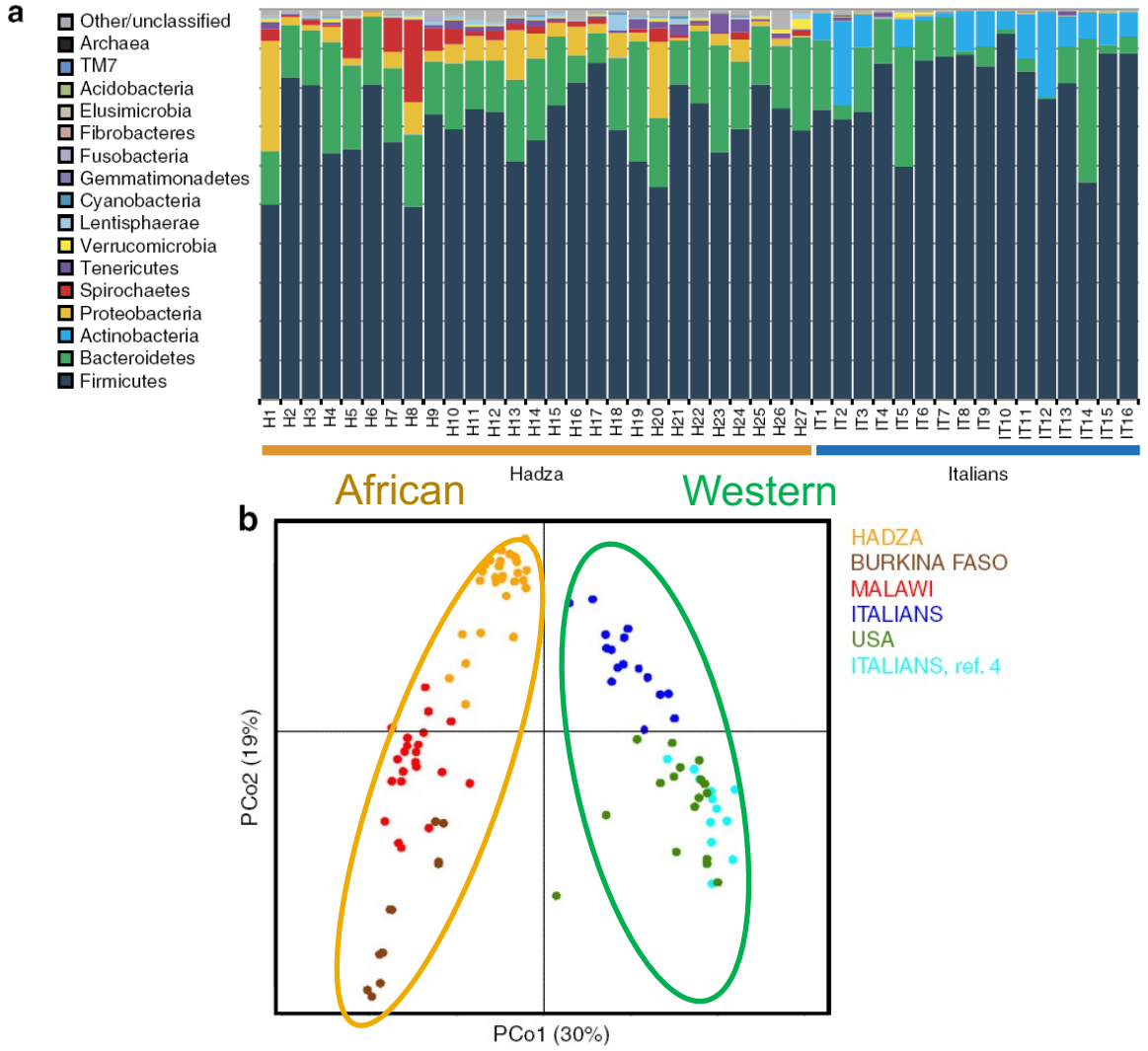


- Beta diversity plot of microbiomes from the lung (GSK study) and other body sites (NIH HMP)
- Lung microbiome is distinct
- Some overlap between oral and lung microbiome
- Skin microbiome is the most variable
- Gut microbiome is most distinct from other body sites

Wang et al. 2016. **European Resp. J.** 47:1082

Microbiome Variation – Life-Style & Diet

Life-style & diet can also affect microbiome composition



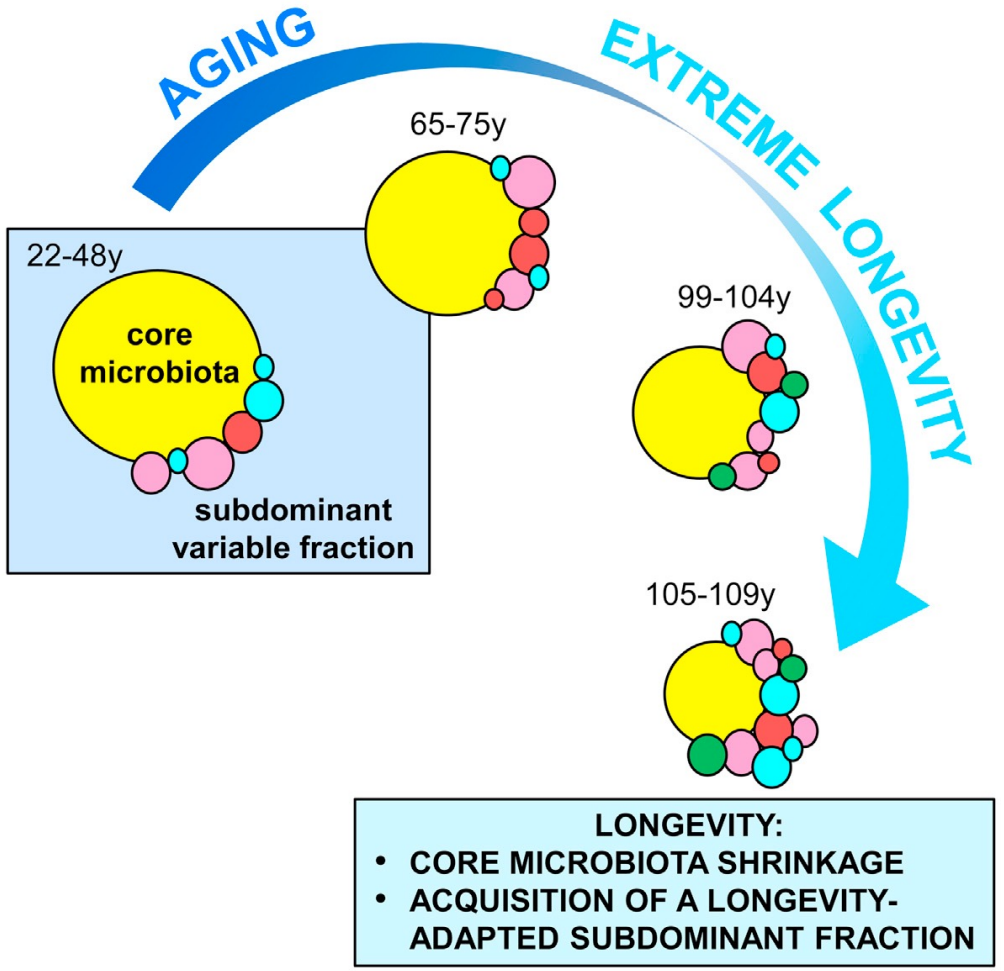
- The Hadza of Tanzania, ancestral hunter gatherers, have more diverse and different microbiomes than contemporary Italians
  - Possibly linked to Hadza's ability to better digest and extract nutrition from fibrous plant foods
- Japanese have carbohydrate-active enzymes originating from marine bacterium to facilitate seaweed digestion (Hehemann et al. 2010. Nature 464:408)
- Diet, life-style effects can complicate biogeography and racial factors (Yadav et al. Gut Pathog. 2016. 8:17)

Schnorr et al. 2014. Nat Commun. 5:3654

Microbiome Variation with Age

Bacterial species diversity is associated with age

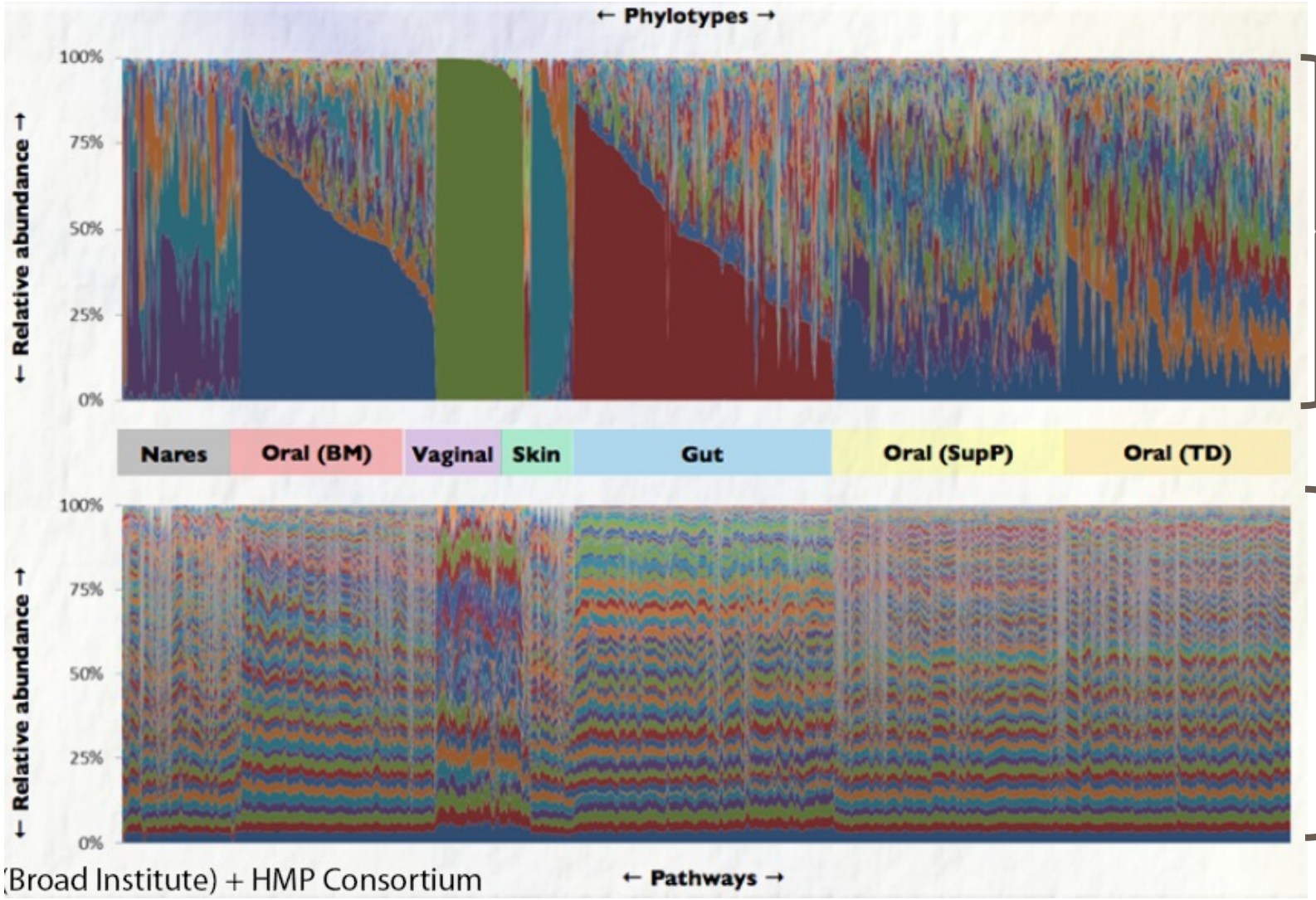
- Neonatal microbiome can vary between caesarian and vaginal birthing (Blaser et al. 2016 Cell Host Microbe 20:558)
- Early exposure to antibiotics might induce longer term shifts in microbiome communities (Bokulich et al. Sci Transl Med. 2016. 8:343ra82).
- A core microbiota accompanies human life, decreasing in abundance along with aging (Biagi et al. 2016. Current Biology 26:1480)
- In longevity, the age-related enrichment of subdominant taxa is boosted
- "Longevity adaptation" seems to involve enrichment in health-associated gut bacteria (e.g., *Akkermansia*, *Bifidobacterium*, and *Christensenellaceae*).



Biagi et al. 2016. Current Biology 26:1480

Microbiome Functional Conservation

While bacterial species may vary in individuals, metabolic potential of the microbiome is conserved



Microbiome Associations with Drug + Disease

Beyond antibiotics, other drugs impact microbiome communities

- Maier et al. 2018 using *in vitro* screens show:
  - 78% of the antibacterials (156 cpds) impacted growth of ≥ 1 species
  - 24% of human-targeted drugs (203 cpds) had anti-commensal activity

ARTICLE

doi:10.1038/nature25979

Extensive impact of non-antibiotic drugs on human gut bacteria

Lisa Maier[1]*, Mihaela Pruteanu[1]†*, Michael Kuhn[2]*, Georg Zeller[2], Anja Telzerow[1], Exene Erin Anderson[1], Ana Rita Brochado[1], Keith Conrad Fernandez[1], Hitomi Dose[3], Hirotada Mori[3], Kiran Raosaheb Patil[2], Peer Bork[2,4,5,6] & Athanasios Typas[1,2]

Maier et al. 2018. **Nature**. 2018. 555:623.

- Jackson et al. 2018 found gut microbiome associations with disease and medication in ~2700 UK Twin cohort:
  - Besides antibiotics, anti-cholinergics, steroid inhalers, acetaminophens, antidepressants (SSRIs) and opioids highly associated with microbiome changes
  - IBD, T2D, constipation, UTIs, food allergies, coeliac disease had the highest disease-microbiome associations

ARTICLE

DOI: 10.1038/s41467-018-05184-7 OPEN

Gut microbiota associations with common diseases and prescription medications in a population-based cohort

Matthew A. Jackson[1,2], Serena Verdi[1], Maria-Emanuela Maxan[3], Cheol Min Shin[1,4], Jonas Zierer[1,5], Ruth C.E. Bowyer[1], Tiphaine Martin[1,6], Frances M.K. Williams[1], Cristina Menni[1], Jordana T. Bell[1], Tim D. Spector[1] & Claire J. Steves[1,3]

Jackson et al. 2018. **Nat Commun.** 9:2655.

Outline

1. Microbiome – why now?

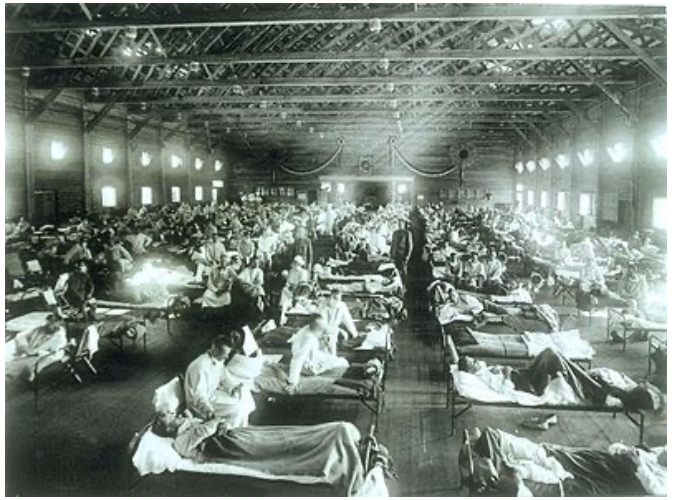
2. **The microbiome, immunity and inflammation**

3. GSK Pharma R&D microbiome activities

The Immune System Balancing Act

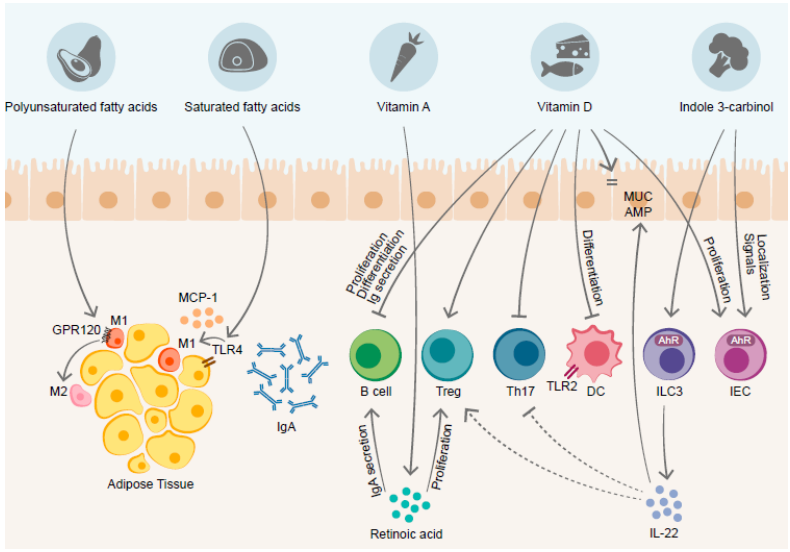
Positive and negative microbial interactions managed by the immune system

- Complex immune pathways have evolved to orchestrate an effective defense against a wide range of ***pathogens*** as well as promoting colonization of ***beneficial microbes*** for dietary energy.



1918 Flu Pandemic

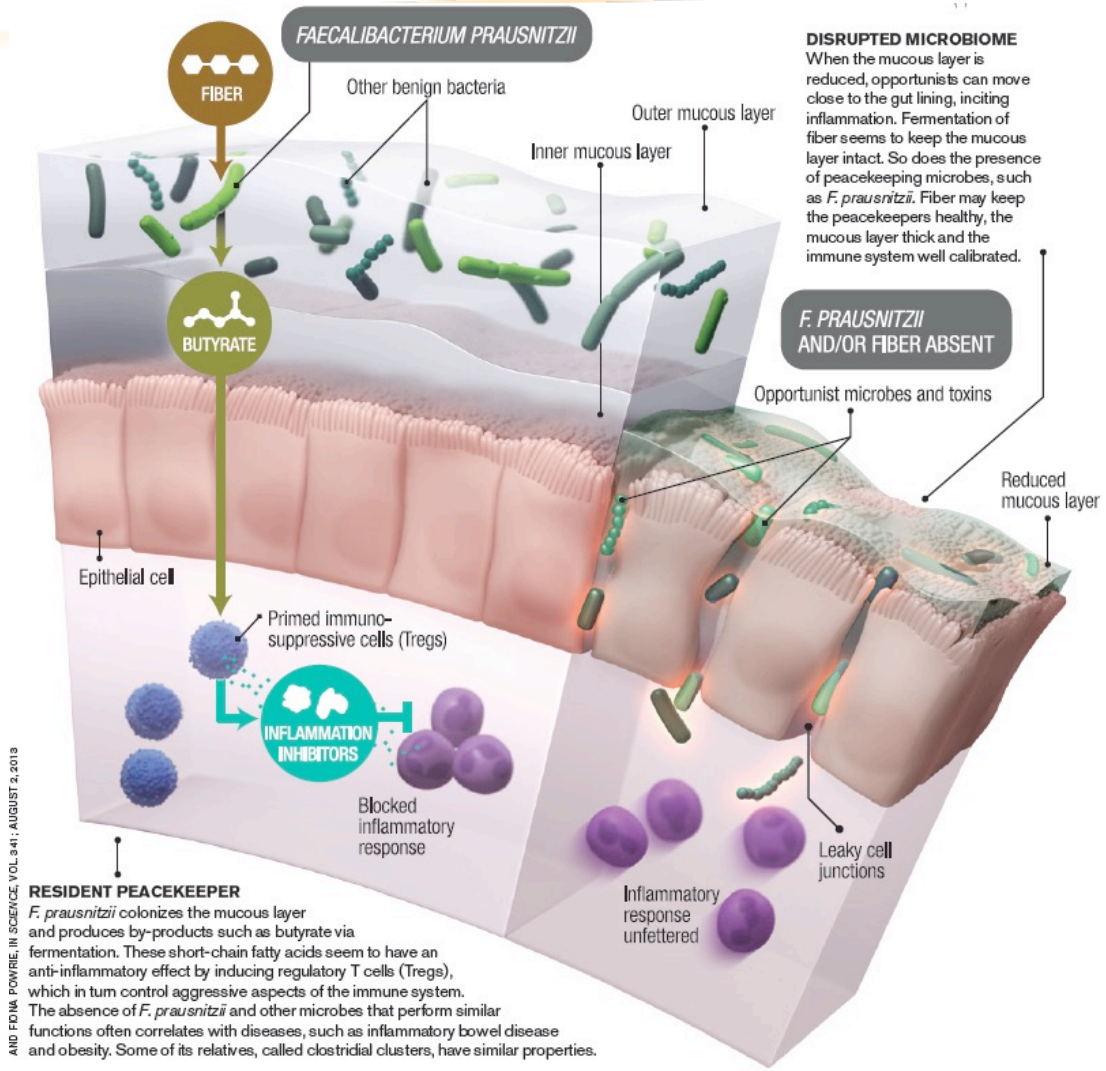
Immune response



Bacterial metabolism of food stuffs

Microbiome as Peace Keepers

Maintaining gut mucosal layers and barriers



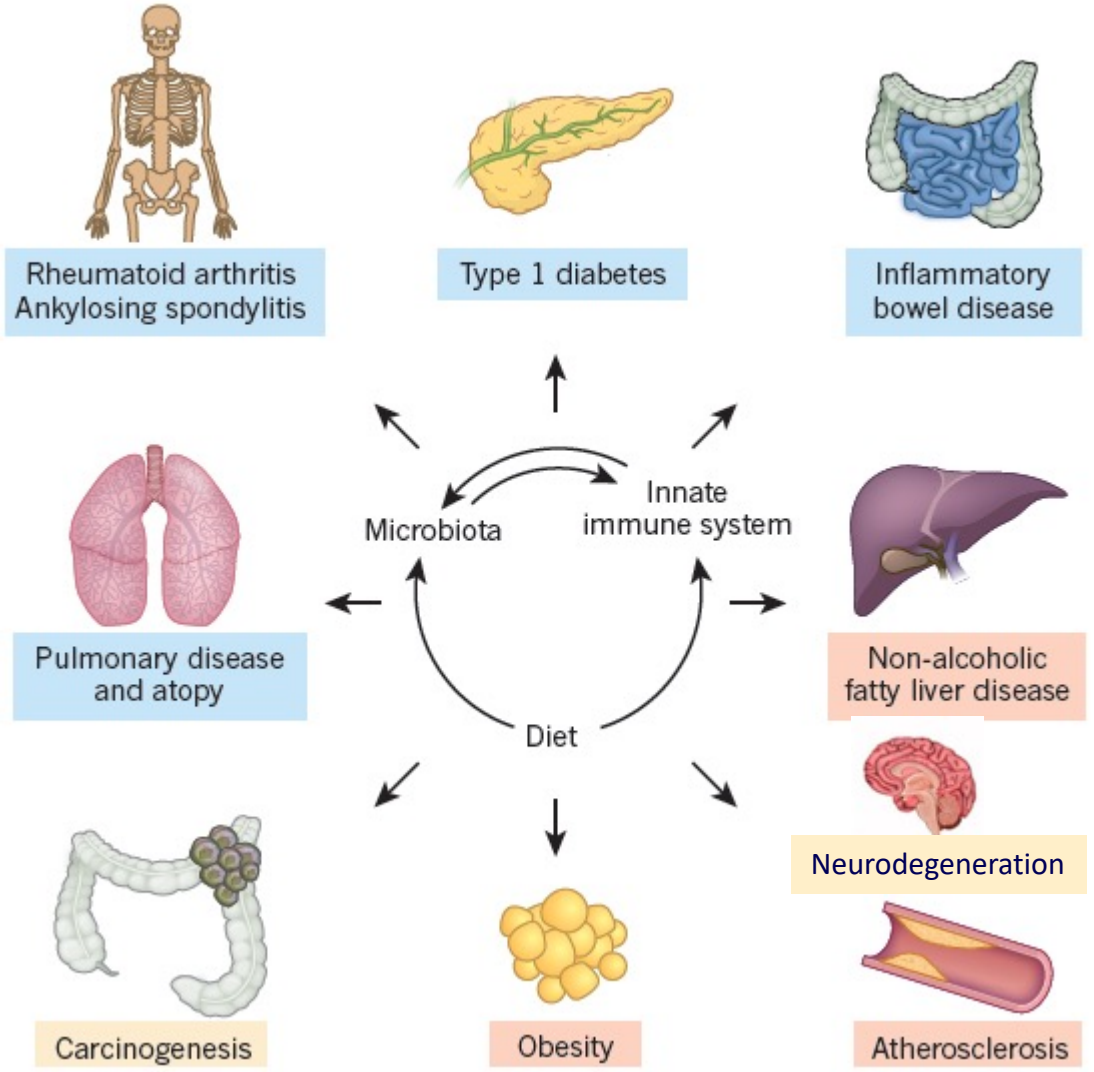
- Certain bacteria strains are associated with “good” gut health and have lower abundance in disease
  - *Faecalibacterium prausnitizii*
  - *Akkermansia muciniphila*
- Dysbiosis comprises gut barrier function
- Bacterial metabolites have a role in promoting gut wall integrity

Velasquez-Manoff. 2015. Nature 518:S4

Microbiome, Inflammation and Innate Immunity

Most diseases have an immuno-inflammation component

- Most disease are driven dysregulation of immuno-inflammation
- Many inflammatory disorders are linked to dysbiosis of the microbiota
- Includes metabolic, neoplastic, neuro-degeneration, auto-immune and auto-inflammatory disorders and infectious disease
- Modulating crosstalk between the host immunity system and the microbiome is a potential therapeutic strategy for multiple diseases



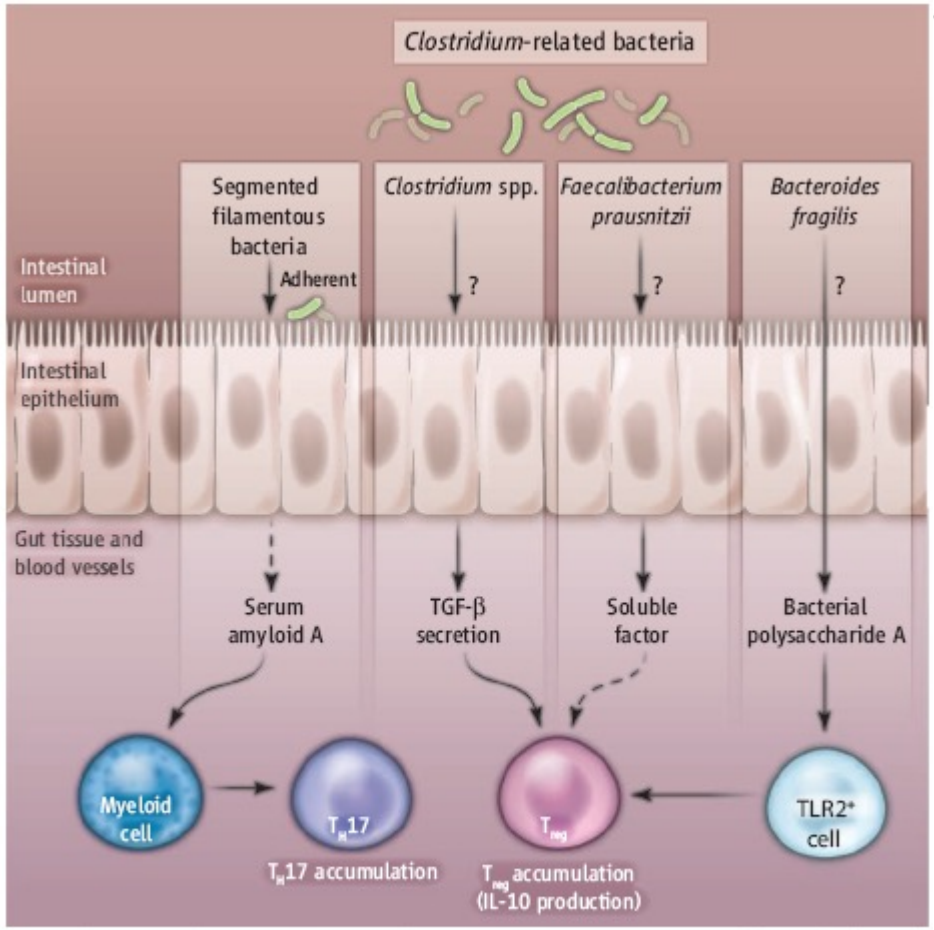
Thaiss et al. 2016 Nature. 535:65

Inflammatory Bowel Disease (IBD)

Multi-factor causes behind ulcerative colitis (UC) and Crohn's disease (CD).

- Genetic component suggested by studies of Ashkenazi Jews (2x higher risk) and twin studies
- Several genes such as FUT2, NOD2 and ATG16L1 interact with gut microbiota
- Microbiome communities in IBD are highly disrupted and dysbiotic
- A custom probiotic mix of Clostridium type IV and XIVa promoted T(regulator) cell accumulation in mice (Atarashi et al. 2011)
- Oral inoculation of Clostridium during early life induced resistance to UC and systemic IgE responses in mice
- Approach of biotech Vedanta / pharma Janssen (J&J)

VEDANTA BIOSCIENCES



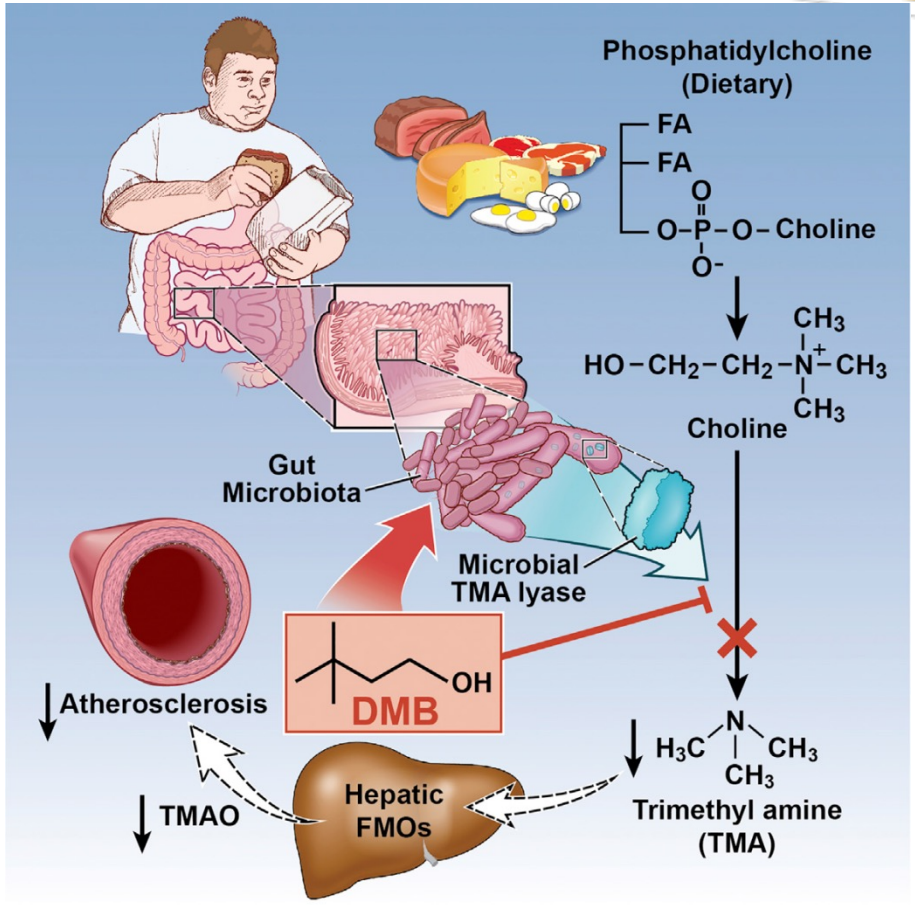
Intestinal bacteria that modulate immune responses. Divergent effects of *Clostridium*-related, Gram-positive bacteria on intestinal CD4+ T cells.

Atarashi Science. 2011 331:337

Gut Microbiome and Cardiovascular Risk

Bacterial metabolite associated with increased coronary artery disease risk

- Elevated levels of the metabolite trimethylanime-N-oxide (TMAO) associated with increased risk for coronary artery disease (CAD)
- Tang *et al.* challenged healthy volunteers with phostatidylcholine diet then measured TMAO levels before and after antibiotic suppression of gut bacteria
  - TMAO was suppressed after antibiotics then rebounded when drugs withdrawn
  - TMAO levels that are associated with adverse CV events are mediated by gut microbiome
- Wang *et al.* showed that inhibiting bacterial lyase reduced TMAO, thus microbiota is a potential target for CAD



Tang et al. NEJM. 2013. NEJM 368:1575

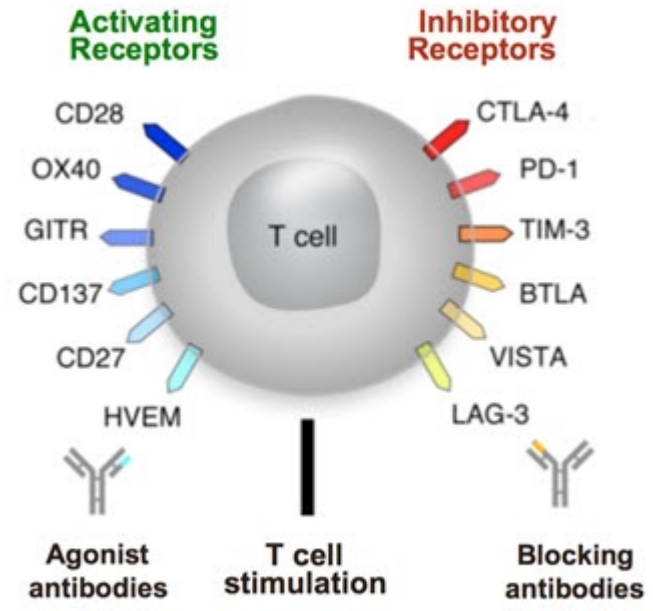
Wang et al. 2015. Cell 163:1585

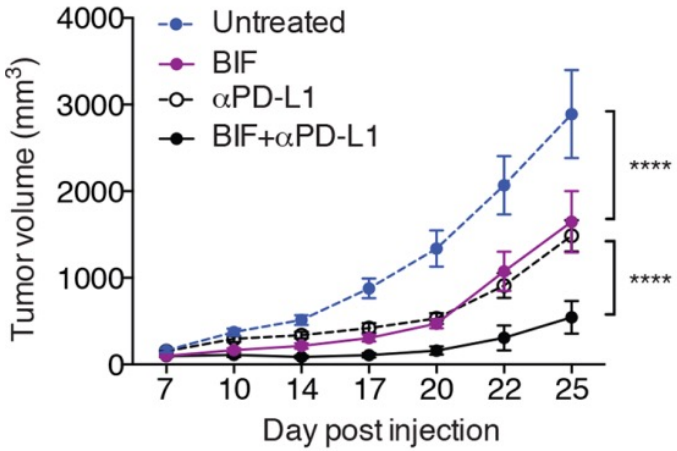
Cancer Immunotherapy Modulated By GI Microbiota

Microbiota mediated responses to onco-immuno-therapies

- New therapeutics that turn the immune system against the tumor are revolutionizing cancer medicine
- In mice and patients, T cell responses specific for *Bacteriodes thetaiotaomicron* and *B. fragilis* associated with CTLA-4 blockade efficacy (Science 2015 350:1079)
  - Tumors in antibiotic-treated or germ-free mice did not respond to CTLA blockade.
  - Defect was overcome by *B. fragilis* gavage, immunization with *B. fragilis* polysaccharides, or transfer of *B. fragilis*-specific T cells
  - Fecal microbial transplantation from humans to mice showed anti–CTLA-4 treatment of melanoma
- Oral administration of *Bifidobacterium* improved tumor control to the same degree as anti–PD-L1 therapy and combination treatment nearly abolished tumor outgrowth (Sivan et al. Science 2015 350:1084)
- Evelo is one example of new "immuno-microbiome" biotechs

EVELO BIOSCIENCES

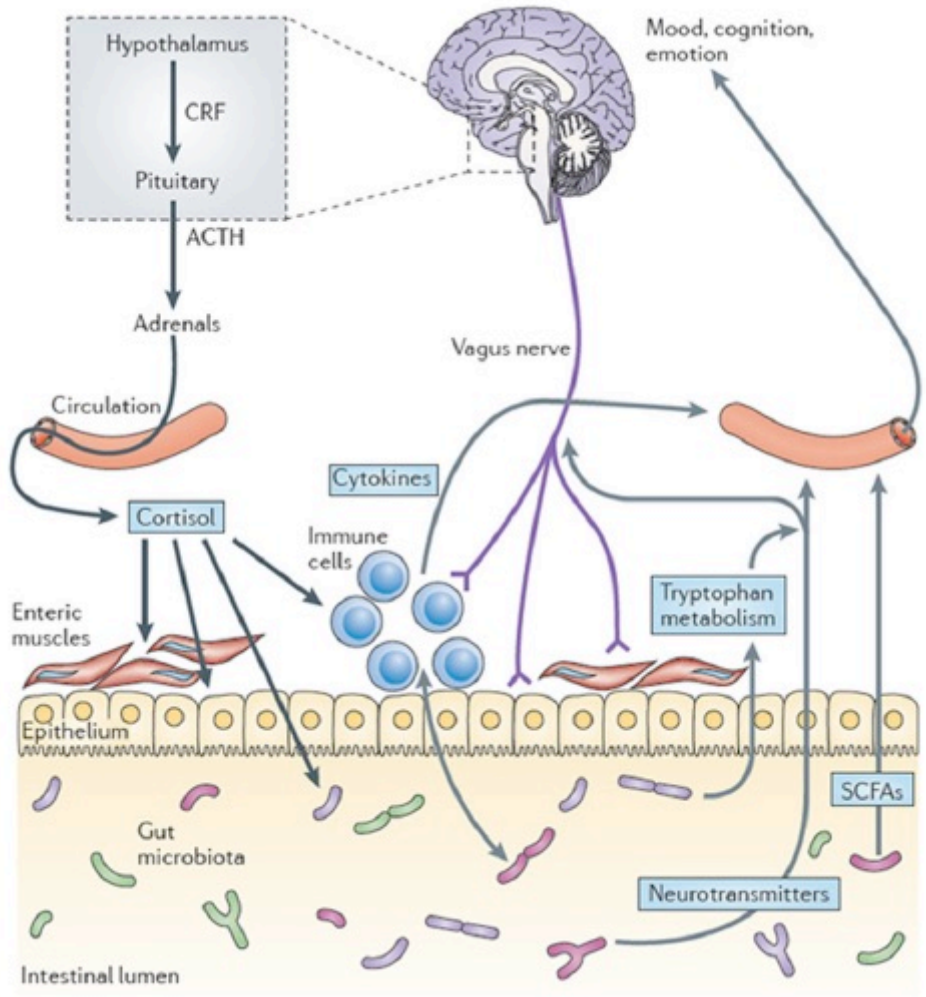




Microbiota-Gut-Brain Axis

Gut bacteria produce neurotransmitters and metabolites that affect the CNS

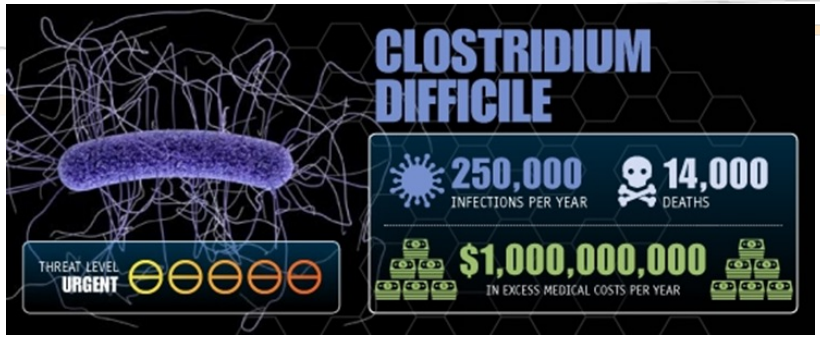
- In mice, vagus nerve activation by gut bacteria reduces stress-induced corticosterone and anxiety- and depression-related behavior (Bravo et al. 2011 PNAS 108:160505)
- *Bacteroides fragilis* mediates behavorial responses in an autism spectrum disorder mouse model (Hsiao et al 2013 Cell 155:1451)
- PD subjects have significantly altered gut microbiomes (Hasegawa et al. 2015 PLoS One 10:e0142164)
- Microbiota from PD patients worsen alpha-synucleinopathy in mouse model (Sampson et al. 2016 Cell 167:1469)
- Potential link between microbiome, immunity and neurological diseases



Petschow et al. Ann. N.Y. Acad. Sci. 2013 1306:1

Fecal Microbial Transplant for Recurrent C. difficile Infection

Radical treatment for C. difficile infections



- Fecal microbial transplant FMT is the infusion of fecal healthy colonic flora into patients after gut sterilization
- Otherwise untreatable patients turn to FMT in desparation
- Has been used to treat recurrent antibiotic-resistant *C. difficile* infections, ulcerative colitis, and chronic constipation (IBS-C)
- NEJM study in 2013 showed FMT more effective than vancomycin in curing patients with recurrent *C. difficile*
- Clinical trials of FMT in other GI tract disorders such as Crohn's disease have been less decisive

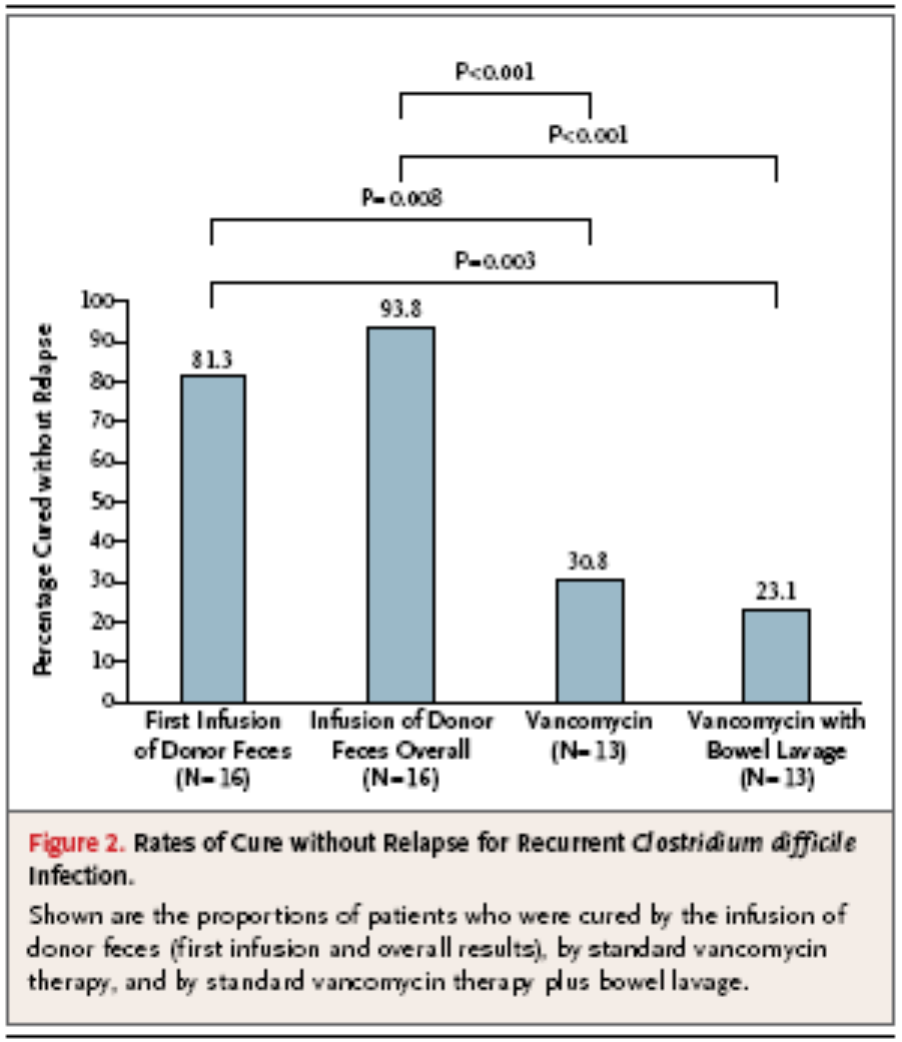


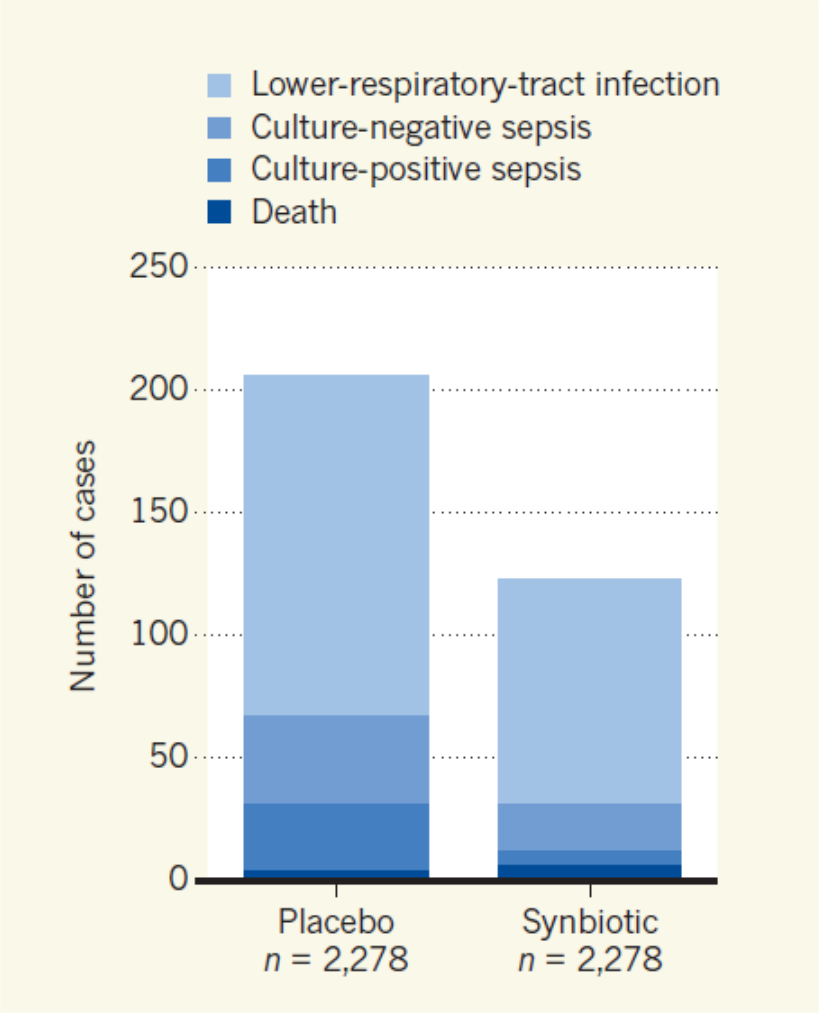
Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Van Nood et al. NEJM. 2013 368:407

Synbiotics Reduce Childhood Sepsis Occurrence

Synbiotics are a combination of probiotics and prebiotics



Tancredi. 2017 Nature. doi:10.1038/nature23540

- Infant sepsis is a major life-threatening disease, particularly for high risk infants (i.e. pre-term births and developing world)
- Large clinical study in rural India (4556 enrolled infants) tested a synbiotic combination of *Lactobacillus plantarum* ATCC-202195 plus fructo-oligosaccharide in a placebo double-blinded trial (Panigrahi et al. 2017. Nature. doi:10.1038/nature23480)
- Synbiotic treated cohort had significantly reduced the incidence of sepsis and lower respiratory tract infection
- Study shows that microbiome modulation can be protective against general bacterial infection

Outline

1. Microbiome – why now?

2. The microbiome, immunity and inflammation

3. **GSK Pharma R&D microbiome activities**

Microbiome Research at GSK Pharma

In 2010, first GSK microbiome matrix team projects initiated

- In house NGS and Computational Biology groups
- Microbiome Collaborative Network (MCN) for sharing science
- Multiple disease areas -- studies initiated and sponsored by the therapy areas
- Clinical studies with microbiome analysis arms focused on disease understanding and therapeutics
  - Infectious disease
  - Metabolic and immuno-inflammatory diseases
  - Respiratory diseases (lung and gut microbiomes)
- External collaborations and publications
- GSK Vaccines and Consumer Health interest as well

Lung microbiome dynamics in COPD exacerbations

AAC Journals.ASM.org

Zhang Wang[1,7], Mona Bafadhel[2,7], Koirobi Haldar[3,6], Aaron Spivak[1], David Mayhew[1], Bruce E. Miller[4], Ruth Tal-Singer[4], Sebastian L. Johnston[5], Mohammadali Yavari Ramsheh[3], Michael R. Barer[3], Christopher E. Brightling[3,6,8] and James R. Brown[1,8]

Microbiome Changes in Healthy Volunteers Treated with GSK1322322, a Novel Antibiotic Targeting Bacterial Peptide Deformylase

Seda Arat,[a,b] Aaron Spivak,[a] Stephanie Van Horn,[c] Elizabeth Thomas,[c] Christopher Traini,[c] Ganesh Sathe,[c] George P. Livi,[c] Karen Ingraham,[d] Lori Jones,[c] Kelly Aubart,[d] David J. Holmes,[d] Odin Naderer,[a*] James R. Brown[a]

OPEN ACCESS Freely available online PLOS ONE

Novel Gut-Based Pharmacology of Metformin in Patients with Type 2 Diabetes Mellitus

Antonella Napolitano[1]*, Sam Miller[2], Andrew W. Nicholls[3], David Baker[3], Stephanie Van Horn[4], Elizabeth Thomas[4], Deepak Rajpal[5], Aaron Spivak[5], James R. Brown[5], Derek J. Nunez[6]

Briefings in Bioinformatics Advance Access published March 24, 2012

BRIEFINGS IN BIOINFORMATICS. page 1 of 18 doi:10.1093/bib/bbs002

Data mining the human gut microbiota for therapeutic targets

Matthew Collison, Robert P. Hirt, Anil Wipat, Sirintra Nakjang, Philippe Sanseau and James R. Brown

Translating the human microbiome

James Brown, Willem M de Vos, Peter S DiStefano, Joël Doré, Curtis Huttenhower, Rob Knight, Trevor D Lawley, Jeroen Raes & Peter Turnbaugh

VOLUME 31 NUMBER 4 APRIL 2013 NATURE BIOTECHNOLOGY

The Microbiome as a Therapeutic Target for Metabolic Diseases

Deepak K. Rajpal[1] and James R. Brown[2]*

DRUG DEVELOPMENT RESEARCH 74 : 376–384 (2013)

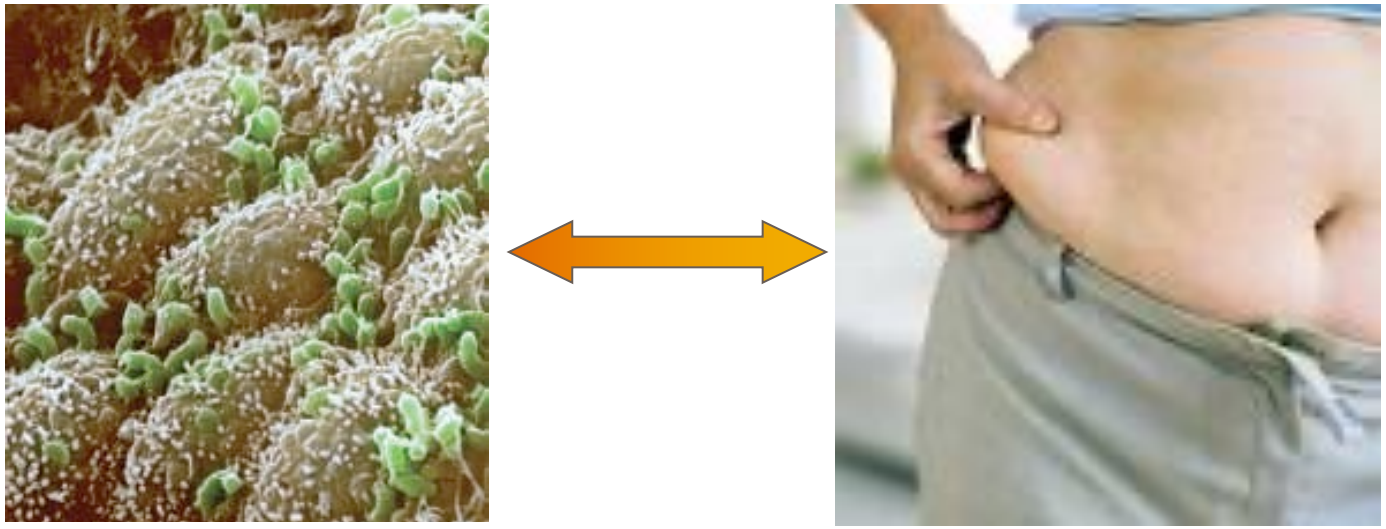
OPEN ACCESS Freely available online PLOS ONE

Host Response to Respiratory Bacterial Pathogens as Identified by Integrated Analysis of Human Gene Expression Data

Steven B. Smith[1,2], Michal Magid-Slav[1], James R. Brown[1*]

Obesity, Type 2 Diabetes Mellitus and the Microbiome

Targeting the microbiome

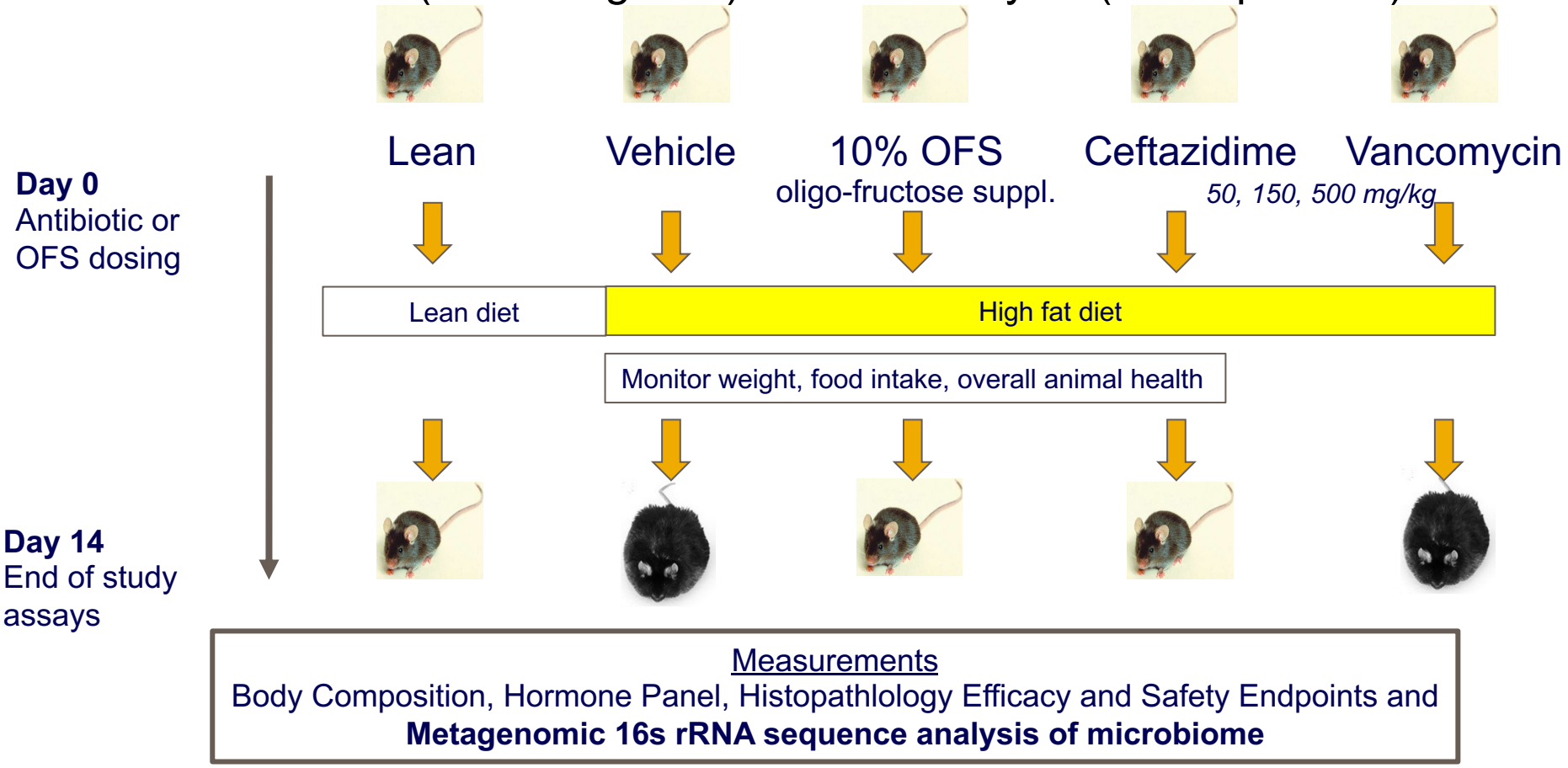


- What is the role of the gut microbiota in human metabolism, obesity and T2DM?
- Gut microbiota are essential for digestion and extraction of nutrients from digested foods.
- Fecal transfer experiments in rodents show that lean and obese phenotypes are transmissible.
- Can we modulate the microbiome to change obesity and T2DM disease states?

Antibiotic Modulation of Obesity and Diabetes

GSK exploratory in vivo study on modulating the microbiome in T2DM model

- Tested two narrow-spectrum antibiotics in diet-induced obesity (DIO) mouse model
- Antibiotics: Ceftazidime (Gram negative) and Vancomycin (Gram positive)

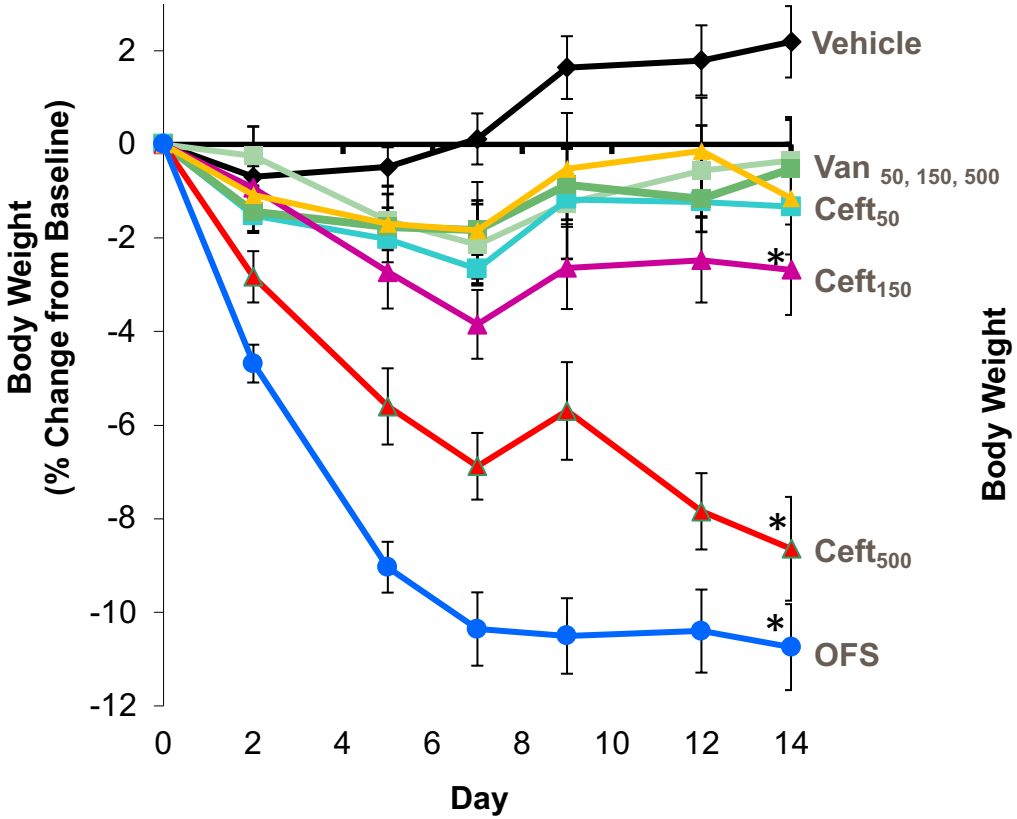


Rajpal et al. 2015. **PLoS One** 10:e0145499.

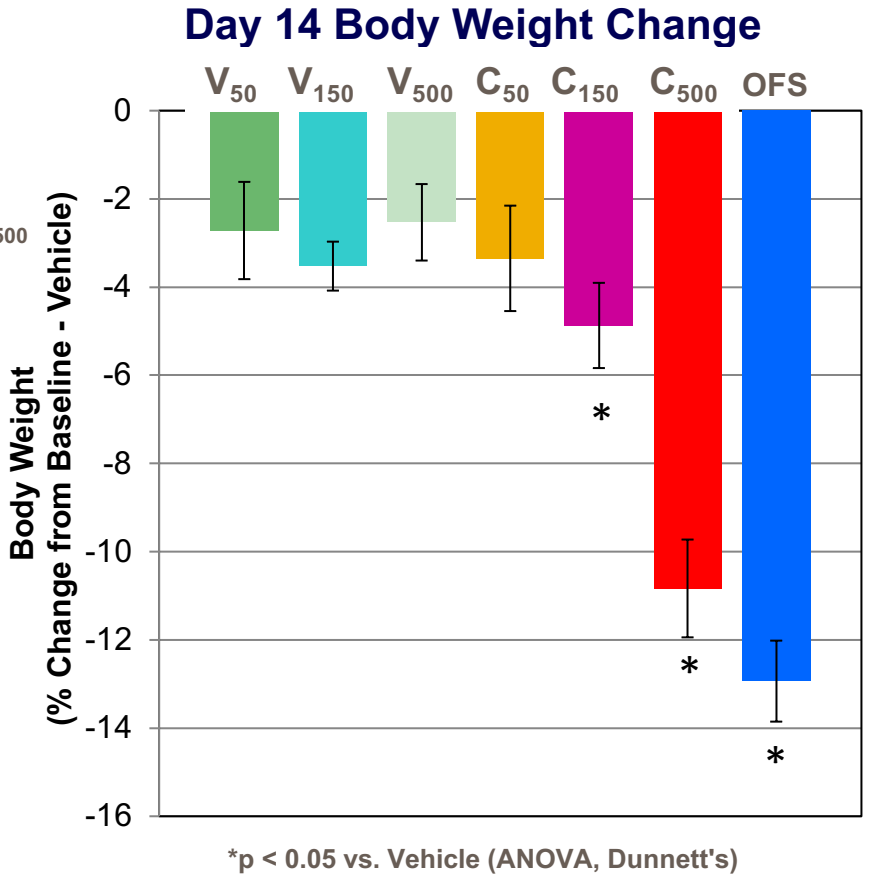
Differential Effects on Body Weight

Ceftazidime and OFS diet reduced body weight but vancomycin did not

- Ceftazidime (Gram negative antibiotic) caused a dose-dependent loss in body weight – highest dose comparable to 10 % OFS diet
- Vancomycin (Gram positive antibiotic) did not result in weight loss



Mean Day 0 Body Wt: DIO: 40.0 g; Lean: 26.6 g



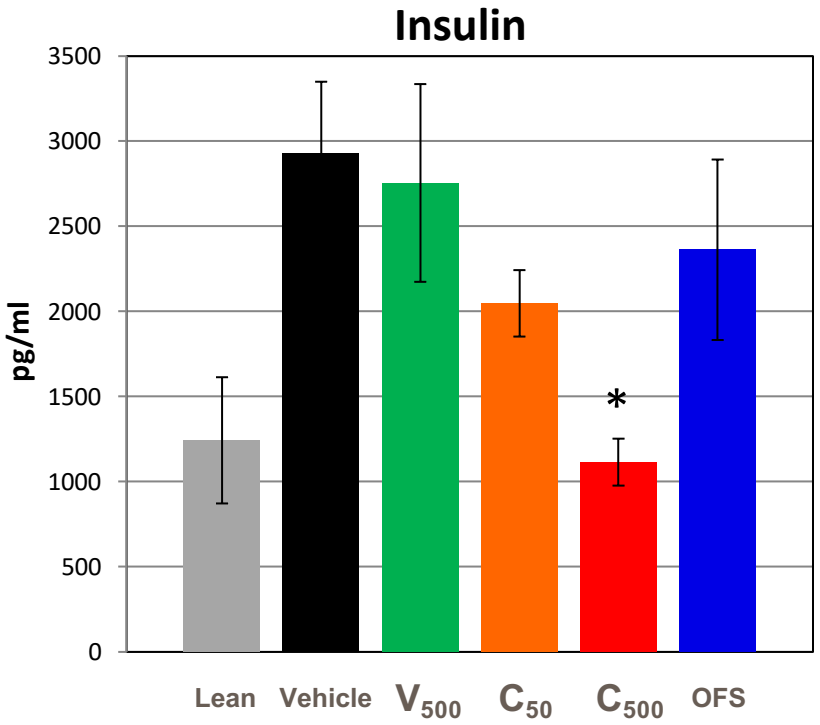
*p < 0.05 vs. Vehicle (ANOVA, Dunnett's)

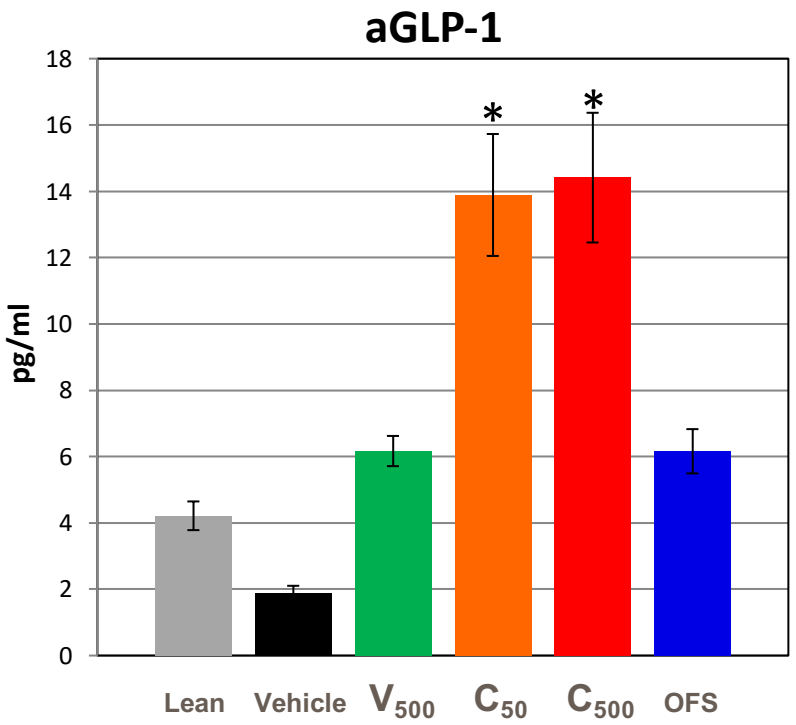
Rajpal et al. 2015. **PLoS One** 10:e0145499.

Modulation of Hormones

Ceftazidime specifically induced hyperglycemic control

- Ceftazidime (CEF) uniquely decreased levels glucose & insulin while elevating active Glucagon-like peptide 1 (aGLP-1) and PYY levels
  - aGLP-1 glucose-dependent stimulator of insulin; decrease food intake
- aGLP-1 agonism by ceftazidime confirmed in rat ZDF diabetes model
- Several aGLP-1 agonist drugs (peptides) are approved for T2DM

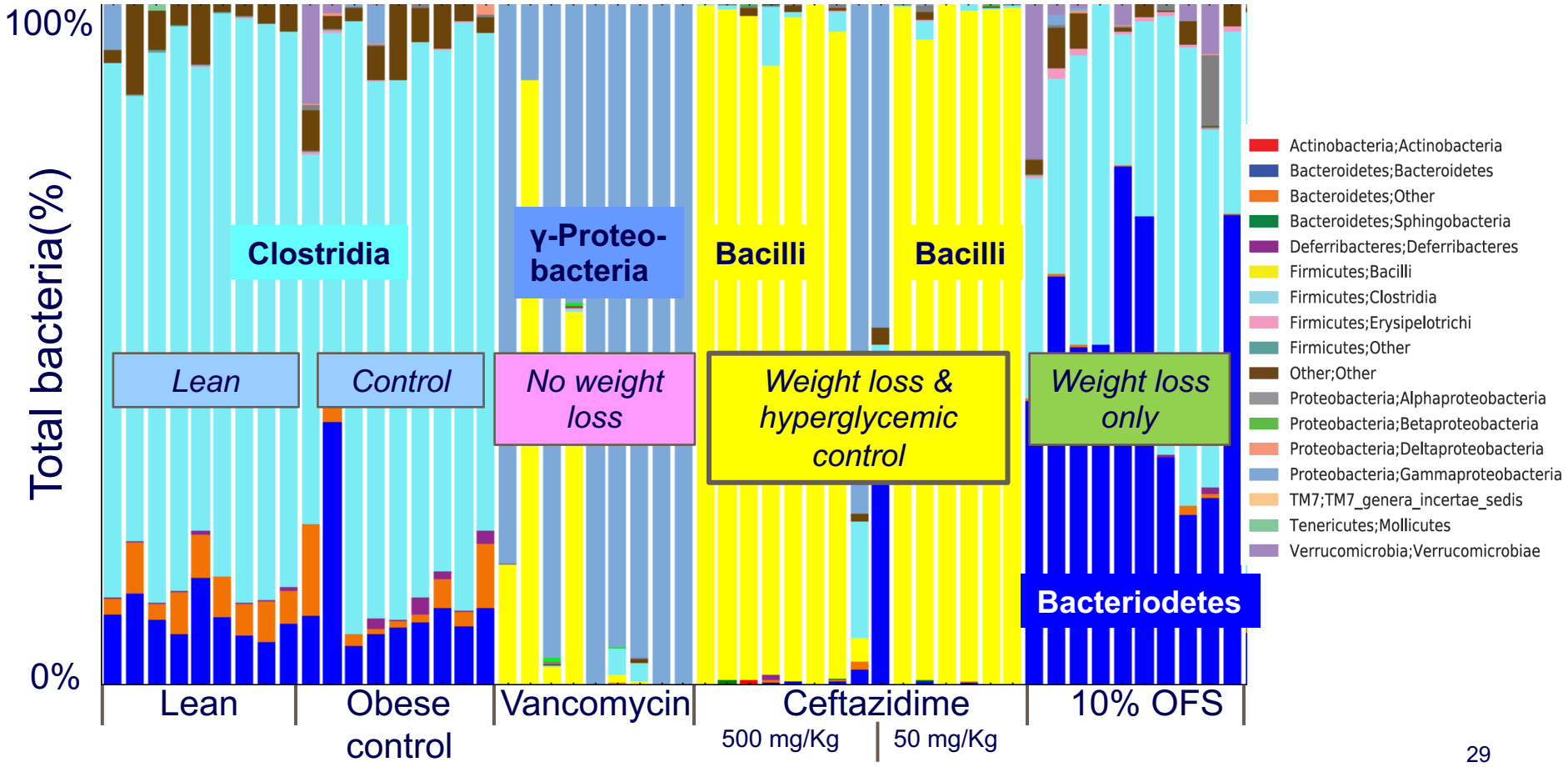




Distribution of Intestinal Bacterial Species

Higher Firmicutes abundance associated with improved hyperglycemic control

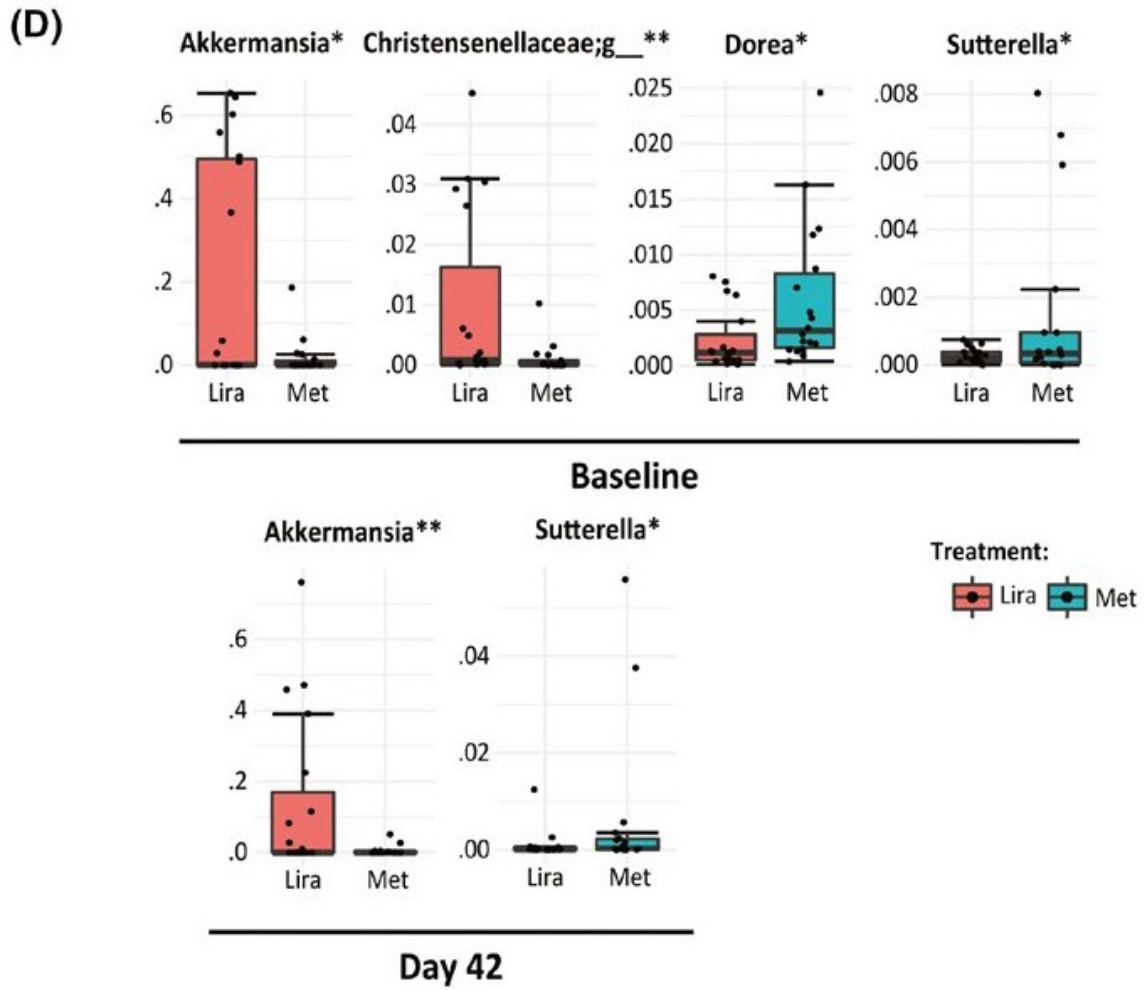
- Reductions in proteobacteria might be related to lower inflammation (i.e. LPS)
- Firmicutes might be producing a more favorable metabolite profile
- Antibiotics are not optimal for longer term dosing for chronic diseases



Rajpal et al. 2015. **PLoS One** 10:e0145499.

Metformin and Liraglutide Change the Microbiome

Microbiome changes to GLP-1 agonist drug, liraglutide



- Microbiome study for T2DM patients on metformin (*n*=18) or aGLP-1 agonist, liraglutide (*n*=19).
- Both drugs differentially changed the microbiome.
- *Akkermansia* sp. were elevated by liraglutide.
  - Genus positively associated with gut barrier homeostasis
- Also significantly correlated with duration of diabetes
  - Higher *Akkermansia* abundances in subjects with short or medium durations vs long term T2DM

Wang et al. 2017. **Endocrinology, Diabetes & Metabolism.** DOI: 10.1002/edm2.9

Antibiotics > Microbiome > Chronic Diseases?

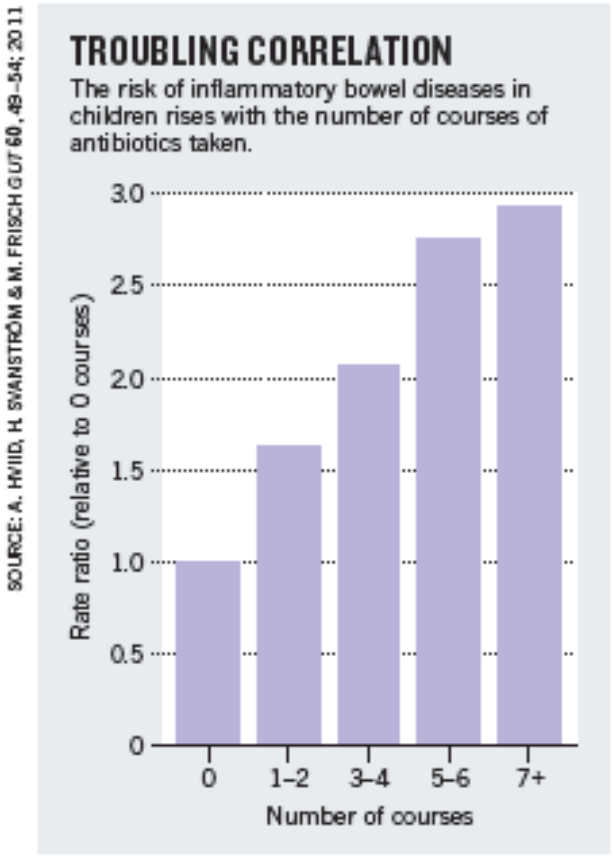
Does overuse of antibiotics in early childhood promote later life chronic diseases?

P. DUREUIL/PHOTOALTO/AGE FOTOSTOCK

Dosed up: could excessive prescription of antibiotics be hampering children's ability to fight disease?

Stop the killing of beneficial bacteria

Concerns about antibiotics focus on bacterial resistance — but permanent changes to our protective flora could have more serious consequences, says **Martin Blaser**.



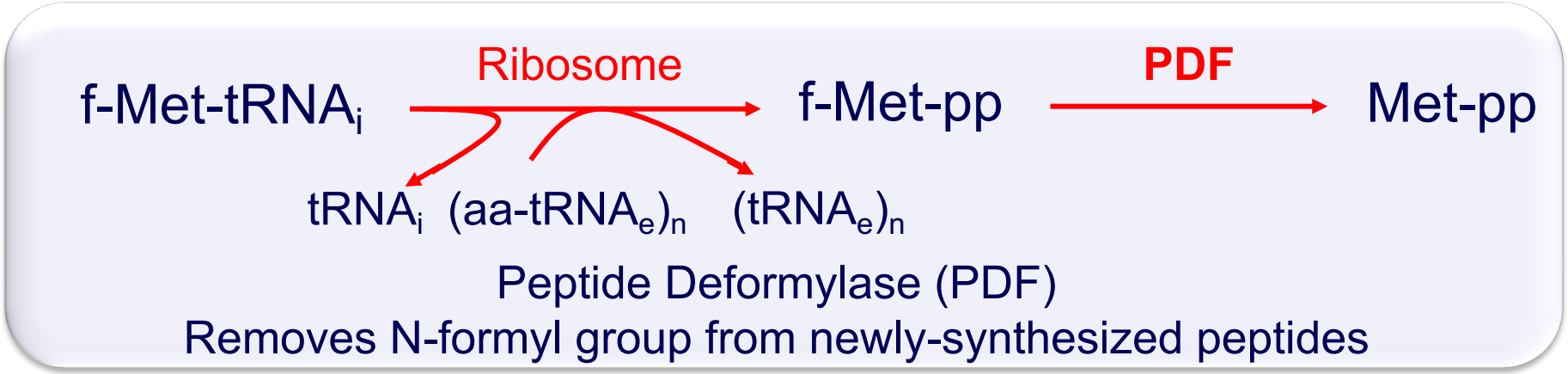
Hygiene hypothesis: "A lack of early childhood exposure to infectious agents, symbiotic microorganisms, and parasites increases susceptibility to allergic diseases by suppressing the natural development of the immune system." Wikipedia

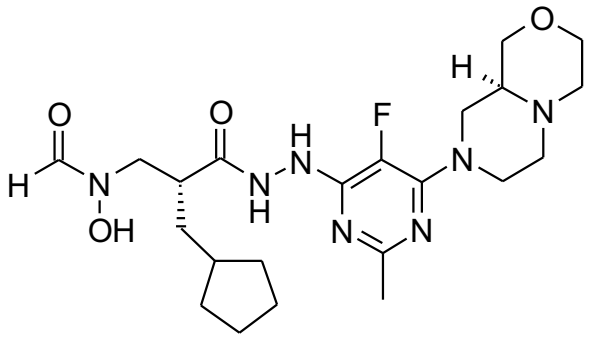
- Average child in developed countries takes 10-20 courses of antibiotics before age 18 yr

Blaser. 2011. Nature. 476:393

GSK1322322 Inhibits Bacterial Peptide Deformylase

Novel mechanism of action and no previous clinical exposure to this drug class





PDF Isozyme	*Ki** (nM)
S. aureus	0.064 ± 0.009
H. influenzae	0.038 ± 0.007
S. pneumoniae	0.011 ± 0.0004

- Novel antibacterial target present in all bacterial organisms
  - Highly conserved active site
- Clinically unexploited
  - Inhibitors should be active against respiratory bacteria resistant to current antibiotics

Phase I GSK'322 Clinical Trial & Microbiome

First controlled human clinical study on the effects of an antibiotic on the gut microbiome

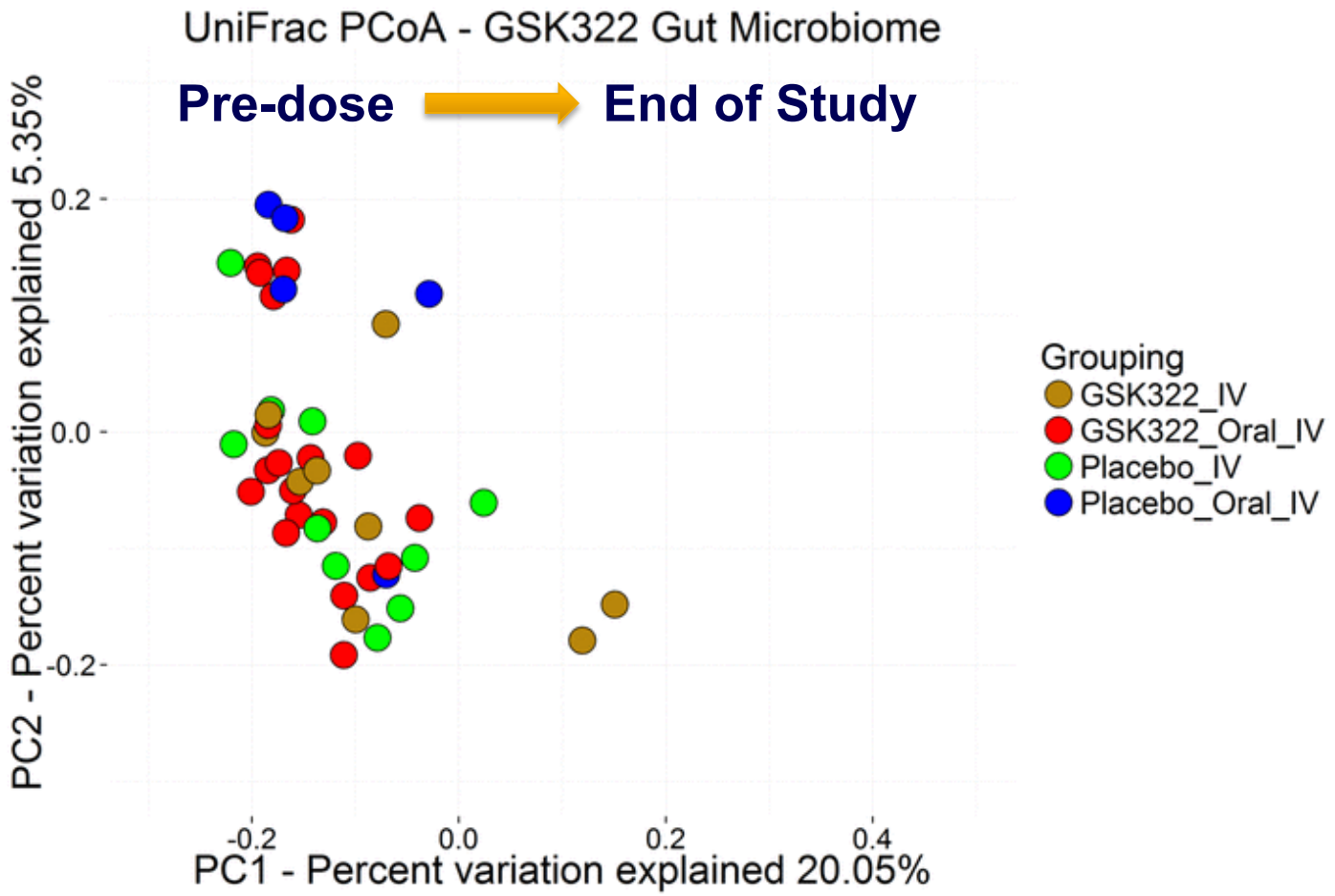
- Phase I, randomized, double-blind, placebo-controlled, dose escalation study (PDF113376) initiated to determine safety, tolerability, and PK profile of GSK'322
- Administered IV as single and repeat dose infusions in 62 healthy subjects
- Three treatment regimens: 1) **placebo**; 2) **IV-only** and; 3) **oral-IV BID (twice daily)**
- Stool samples were collected with consent at **pre-dosing** and **end-of-study** for Illumina DNA sequencing of microbiome 16S rRNA V4 region (Total *n* = 119 samples)

Arat et al. 2015. ***Antimicrobial Agents and Chemotherapy*** 59:1182

Drug Effects on Overall Microbiota Diversity

Drug dosing regimen matters

- Beta-diversity is a relative index of microbial community diversity
- ***Oral/IV*** dosing regimes notably changed the baseline microbiome while ***IV only drug dosing and placebo*** induced minimal change

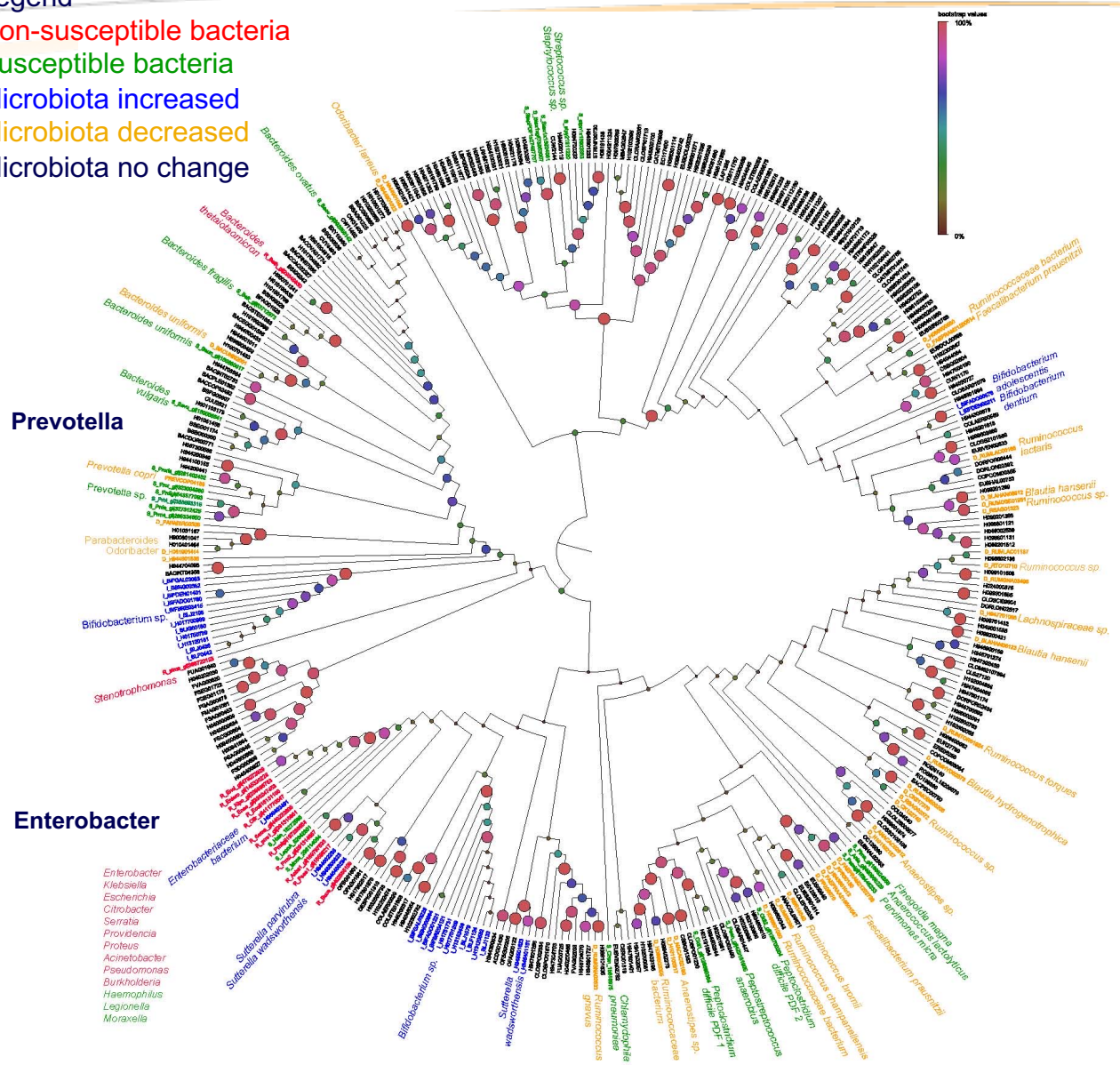


Arat et al. 2015. ***Antimicrobial Agents and Chemotherapy*** 59:1182

In vitro vs *In vivo* Activity of Oral/IV GSK'322

Preclinical studies could be predictive of drug effects on the human microbiome

Legend
Non-susceptible bacteria
Susceptible bacteria
Microbiota increased
Microbiota decreased
Microbiota no change

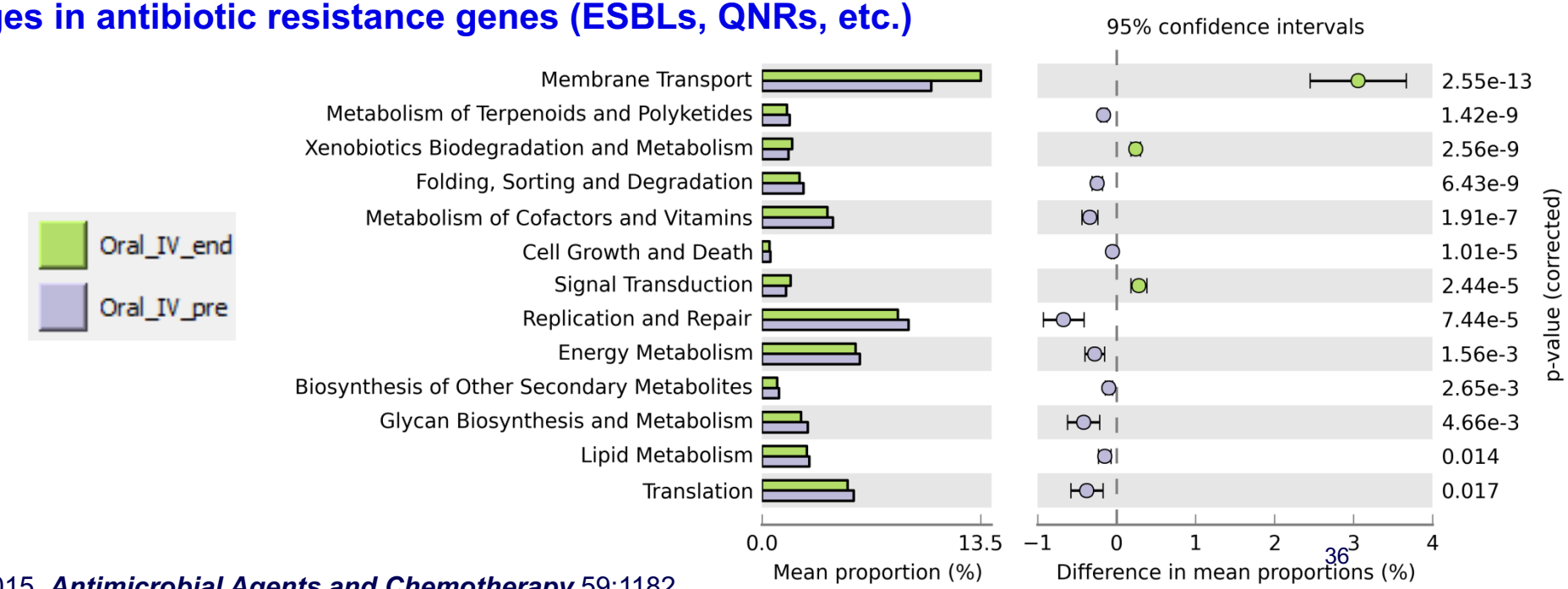


- Phylogeny of PDF proteins in pathogens and microbiota
- Firmicutes, Bacteriodetes decreased overall
- Proteobacteria, Bifidobacterium increased
- Enterobacter MICs > 8 and increased in gut
- Prevotella had low MICs and gut Prevotella decreased
- Many species were not significantly changed

Inferred Metagenomic Changes

GSK'322 does not promote wide-spread selection for anti-biotic resistance

- Infer functional changes from 16s rRNA species profiles using PICRUSt (Langille et al. 2013. Nature Biotech. 9:814) and STAMP (Parks & Beiko. 2010. Bionformatics 26:715)
- Oral_IV pre vs Oral_IV end – changes related to antibiotic stress
  - **Increase in membrane transport – i.e. Efflux pumps**
  - **Increase in xenobiotic biogradation and metabolism**
  - **Decrease in overall metabolism and cell growth**
  - **No significant changes in antibiotic resistance genes (ESBLs, QNRs, etc.)**



Arat et al. 2015. ***Antimicrobial Agents and Chemotherapy*** 59:1182

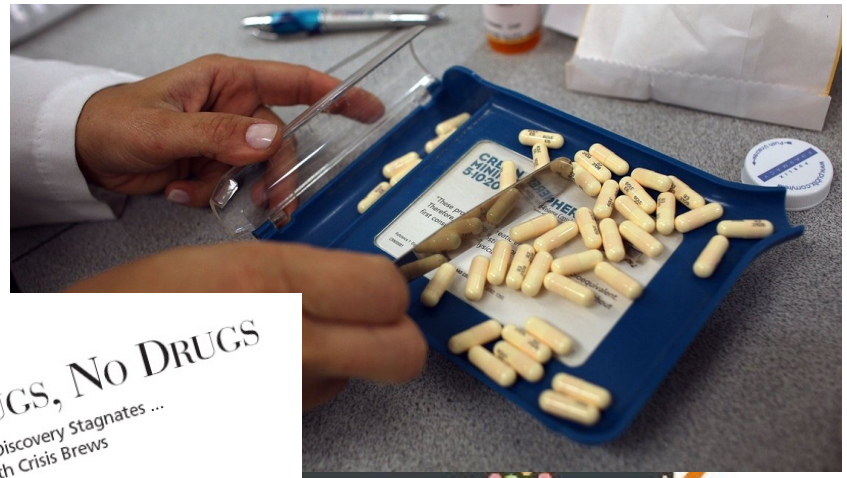
Antibiotics, Microbiome and Human Health

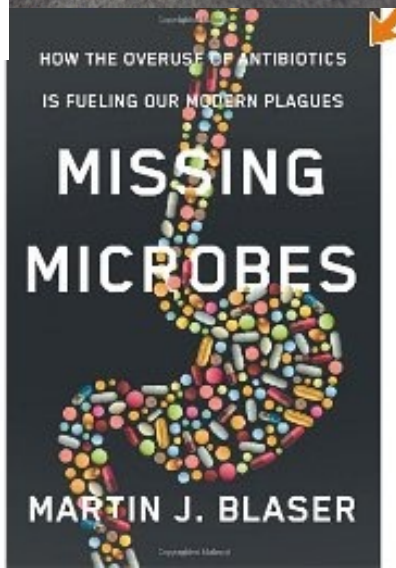
Target and drug delivery regimen need to be considered

- Global healthcare urgency for new classes of antibiotics
- Also growing evidence that long term exposure to antibiotics has negative effects on human health
- GSK study suggests antibiotic properties are important
  - Delivery regime – Oral vs IV-only
  - Specific versus broad bacterial targets
- Microbiome studies planned for future antibiotic trials to assess risk vs benefits

"We are in danger of returning to a pre-antibiotic era"

Royal Society Policy Document, July 2008.





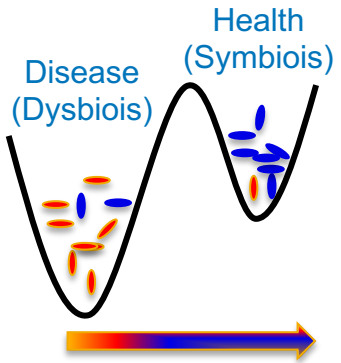
Overview of Microbiome Therapeutic Strategies

Targeting either the "messenger" or the "message"

Manipulate Microbial Ecology (The Messenger)

Alter microbial ecology and biochemistry using:

- Fecal material transplant (FMT)
- Highly selective small molecule and biological inhibitors of bacterial species
- Engineered probiotics
- Prebiotics
- Vaccines
- Combinations of above

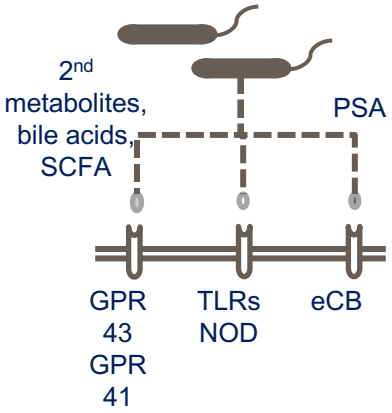


Rajpal & Brown 2013 **Drug Development Research** 74:376

Modulate Human-Microbe Crosstalk (The Message)

Target human receptors that interact with the microbiota and/or their products via:

- Metabolite-like molecules
- Bacterial components
- Build target evidence for specific diseases using human genomics and genetic data



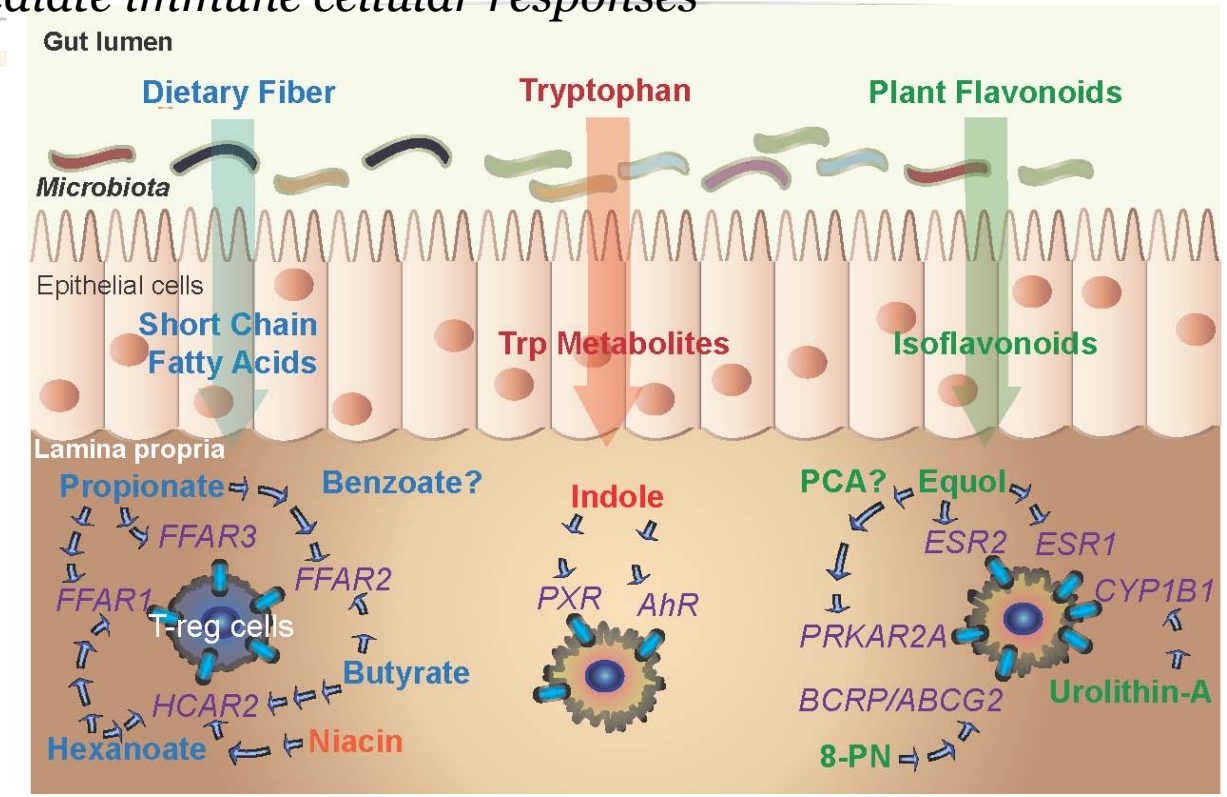
Challenges

- Establish confidence in mechanism of action
- Prove superiority to existing therapeutics
- Fulfills manufacturing, regulatory and other standards for a consistent product

Targeting Human Host-Microbial Crosstalk

Bacterial metabolites mediate immune cellular responses

Dr. Somdutta Saha, Early Talent PDF

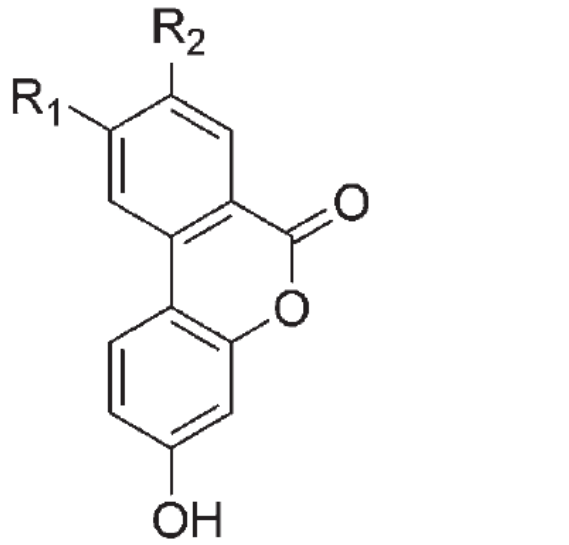


Saha et al. 2016. **Drug Discovery Today** 21:692

- Endogenous bacterial metabolites are known to be well-tolerated
- Evolution has optimized metabolite-receptor interactions
- Metabolites are known modulators of immune and inflammation pathways
- Many successfully launched drugs have “metabolite-like” properties (Dobson et al. 2009 **Drug Discovery Today** 14:31)

Example: Metabolite Modulation of Immunity

Bacterial metabolism of dietary plant fibers can mediate immune responses



UA	R_1=H; R_2=OH
UB	R_1=H; R_2=H
UC	R_1=OH; R_2=OH
MUA	R_1=H; R_2=OCH_3
MUC	R_1=OCH_3; R_2=OCH_3

Fig. 1 Structures of examined urolithins and their methylated derivatives: urolithin A (**UA**), urolithin B (**UB**), urolithin C (**UC**), 8-methyl-*O*-urolithin A (**MUA**), and 8,9-di-methyl-*O*-urolithin C (**MUC**).

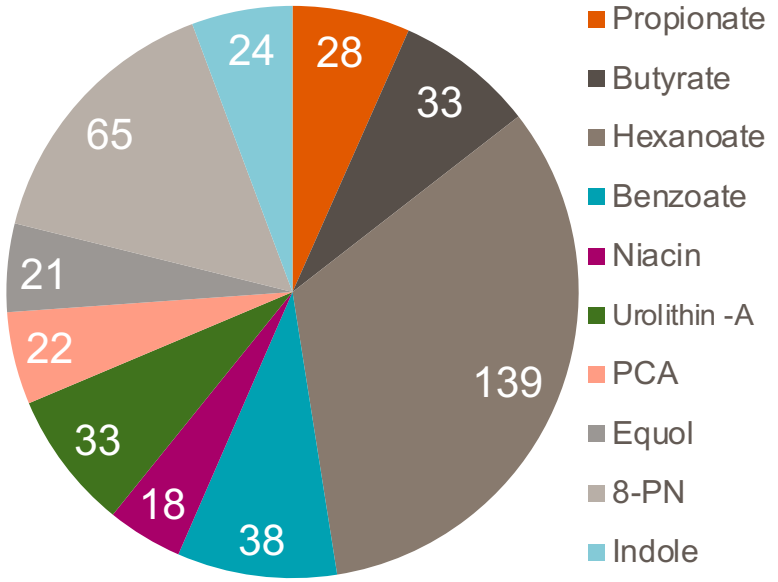
- Urolithins are gut bacteria produced metabolites of ellagitannins derived from plants, fruits and nuts
- Urolithins modulate immune functions of neutrophils
- Anti-cancer effects on prostate cancer cell types
- Bacterial metabolism contributes to the beneficial health effects of ellagitannin-rich medicinal plant materials and food products

Piwowarski JP et al. 2014 Planta Med 80:887

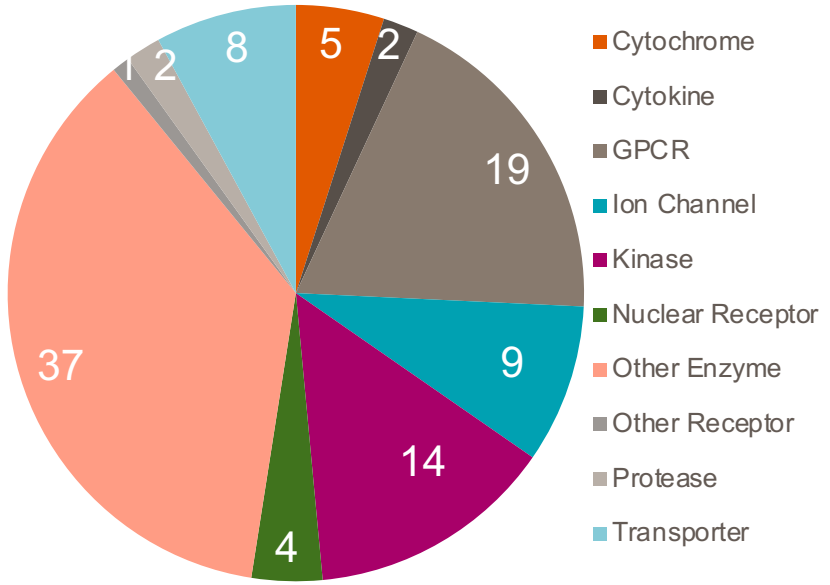
Metabolite-mimic Occurrences and Target Classes

Distributions of metabolites and targets in GSK databases

(a)



(b)



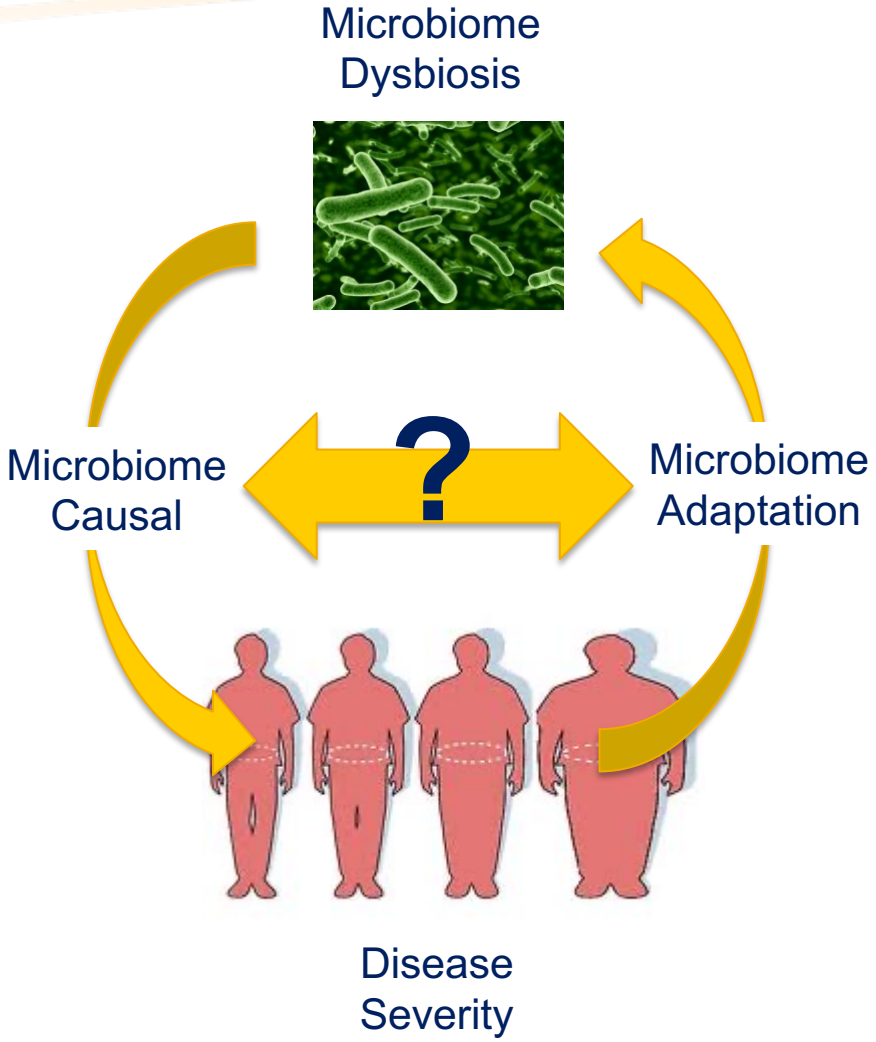
421 “metabolite-mimics” found in the GSK compound collection
(Tanimoto structural similarity ≥ 0.8)

101 human receptor ligand relationships based on historical assay data

Saha et al. 2016. **Drug Discovery Today** 21:692

Challenge: Microbiome-to-Disease Causality?

The Elephant-in-the-Room: Is the Microbiome Hype or Promise



- Many opportunities for new medicines based on modulating the human-microbe interface.
- However, are changes in the microbiome causing disease or merely adaptations to the disease environment?
- What human host genes / pathways link microbiome with disease pathology?
- Can manipulation of the microbiome reverse a disease phenotype?
- Are microbiome therapies better than current standard of care?

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- All studies were conducted after review by the GSK Institutional Animal Care and Use Committee and in accordance with the GSK Policy on the Care, Welfare and Treatment of Laboratory Animals.
- The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents.