Targeting the Human Host-Microbiome Interface in Metabolic Disease

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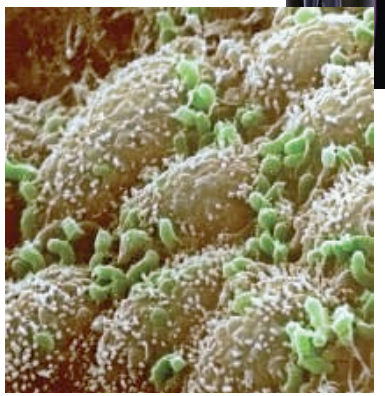
Computational Biology, Target Sciences

09/27/2018



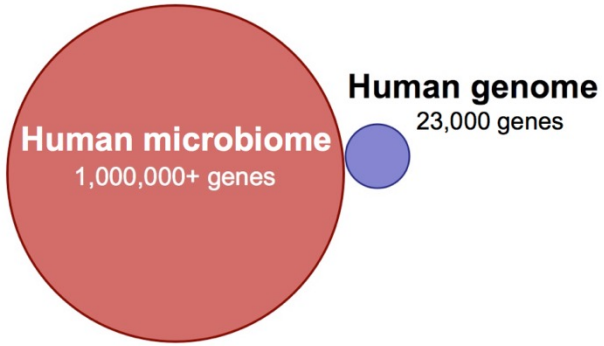
Outline

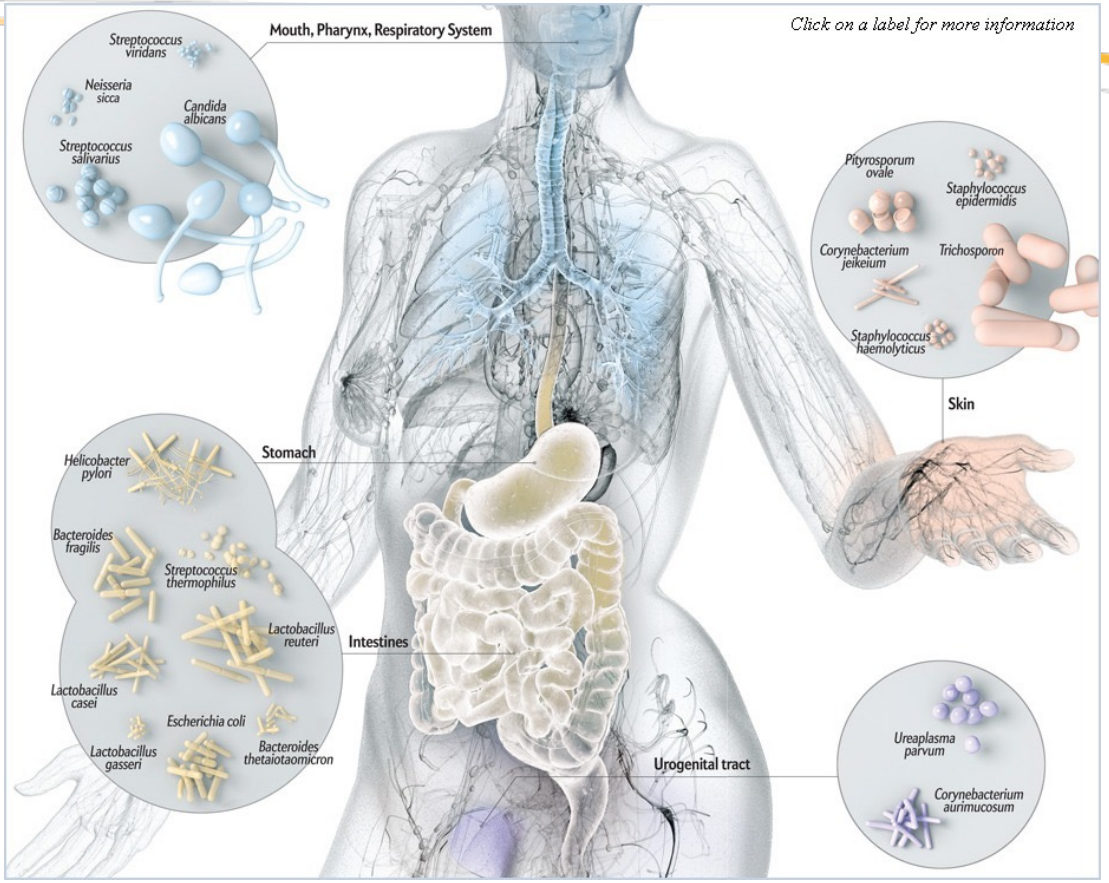
1. **Defining the “normal” vs “disease” microbiome**
2. Modulation of the microbiome in obesity/diabetes *in vivo* models
3. Microbiome and clinical pharmacology
4. Bacterial metabolites as immuno-modulators

The Human-Microbial Ecosystem

We are not alone…

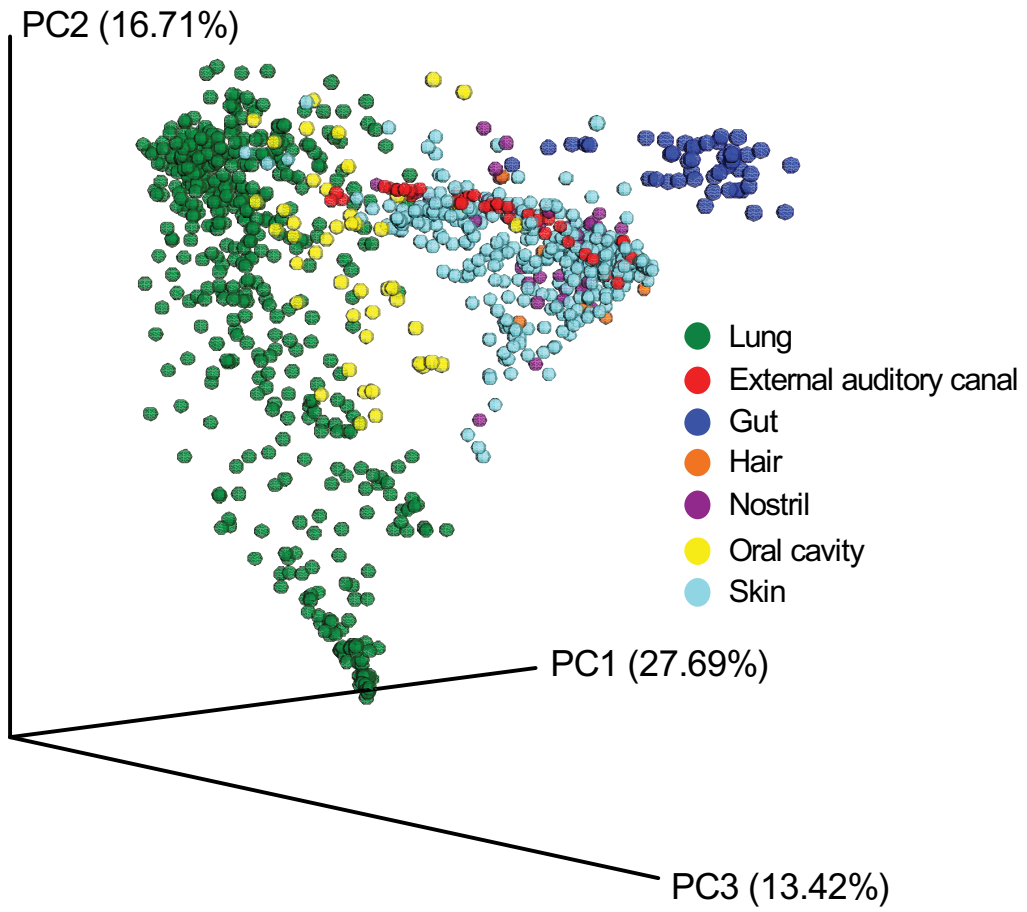
- **Microbiota** –10^{14} bacteria in the gut
  - 10 times more gut bacteria than human cells
  - 100's to 1000 species
- **Microbiome** – 100 times more bacterial genes than in human genome
- Microbiome implicated in many chronic diseases





“Healthy” Microbiome Variation – Body Site

Microbiome composition varies by body site

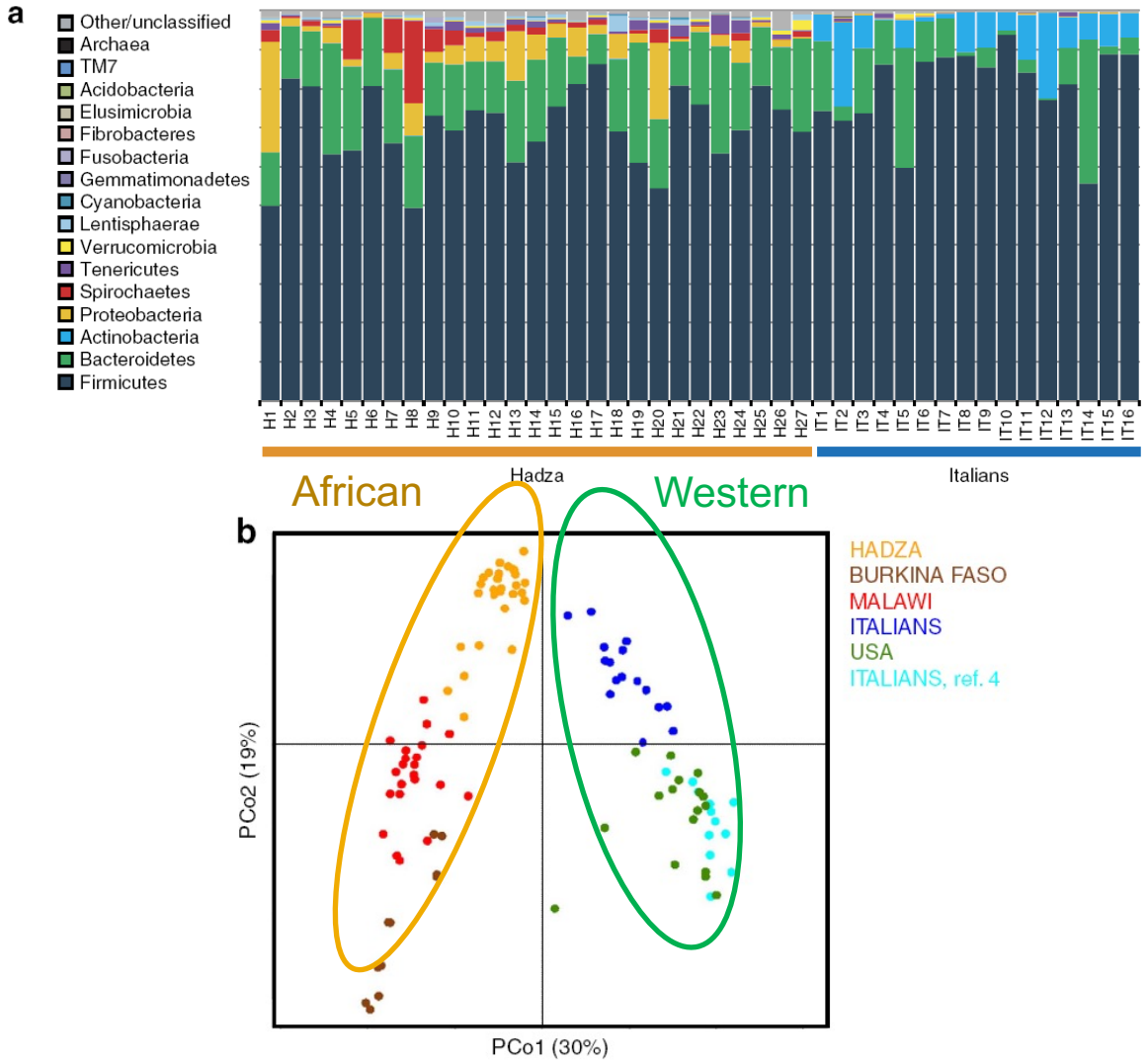


- Beta diversity plot of microbiomes from the lung (GSK study) and other body sites (NIH Human Microbiome Project)
- Lung microbiome is distinct
- Some overlap between oral and lung microbiomes
- Skin microbiome is the most variable

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

Microbiome Variation – Life Style & Diet

Life style & diet affect microbiome composition



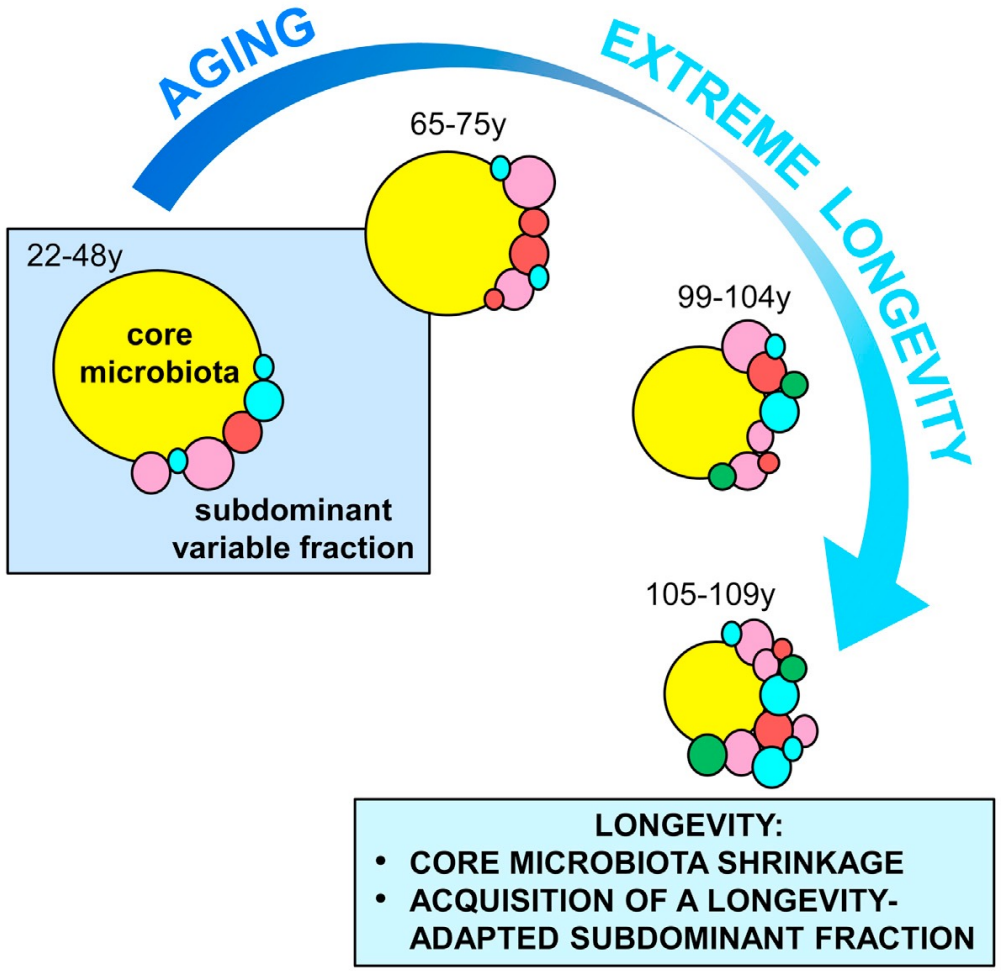
- The Hadza of Tanzania, ancestral hunter gatherers, have more diverse and different microbiomes than contemporary Italians
- High microbiome diversity possibly linked to Hadza's ability to digest and extract nutrition from fibrous plants
- Japanese have carbohydrate-active enzymes originating from marine bacterium for seaweed digestion (Hehemann et al 2010 **Nature** 464:408)

Schnorr et al. 2014. **Nature Communications** 15:3654

Microbiome Variation with Age

Bacterial species diversity is associated with age

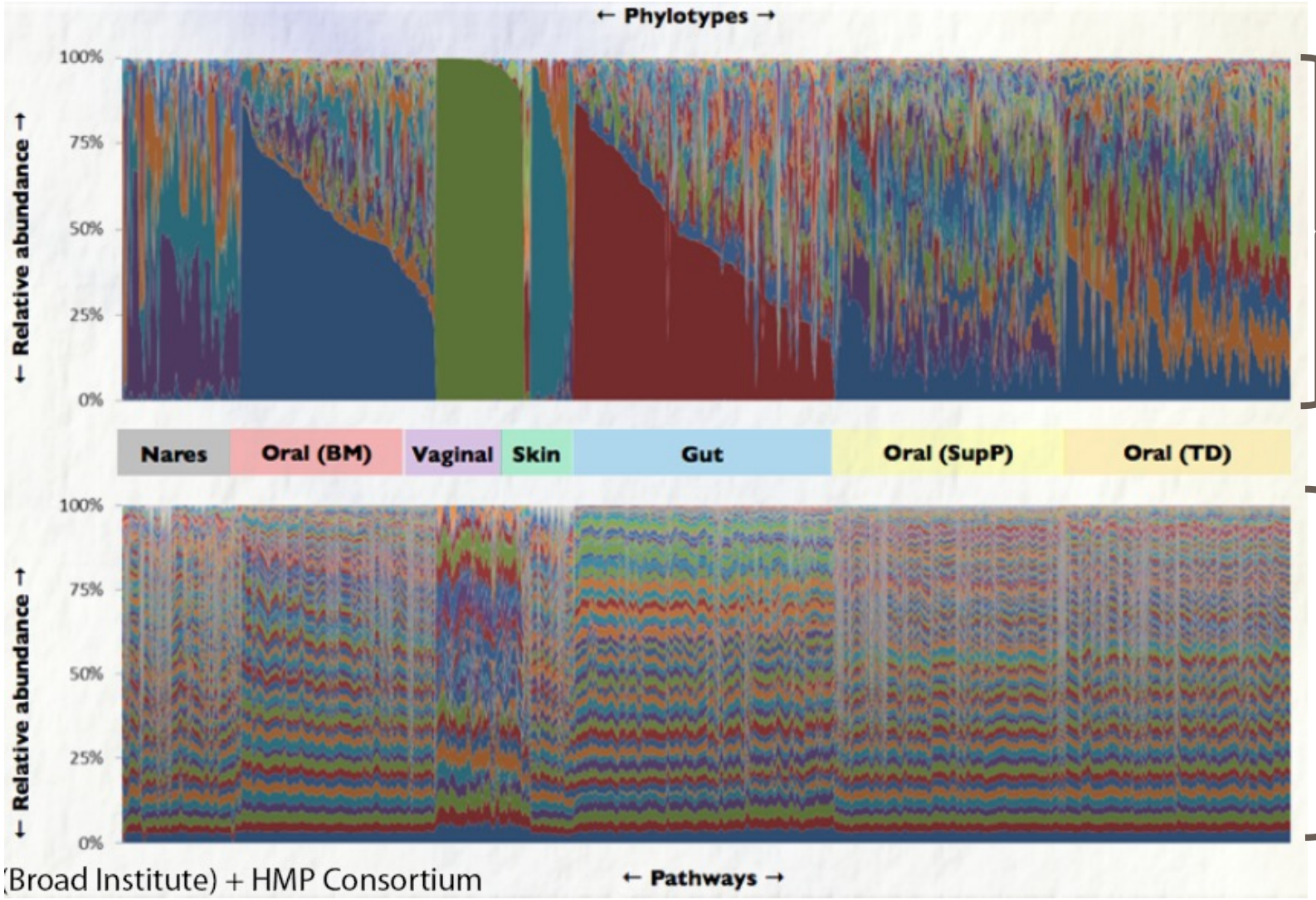
- Neonatal microbiome can vary between caesarian and vaginal birthing
- A core microbiota accompanies us throughout our lives, decreasing in abundance along with aging
- In longevity, the age-related enrichment of subdominant taxa is boosted
- "Longevity adaptation" seems to involve enrichment in health-associated gut bacteria (e.g., *Akkermansia*, *Bifidobacterium*, and *Christensenellaceae*).



Biagi et al. 2016. **Current Biology** 26:1480

Microbiome Functional Conservation

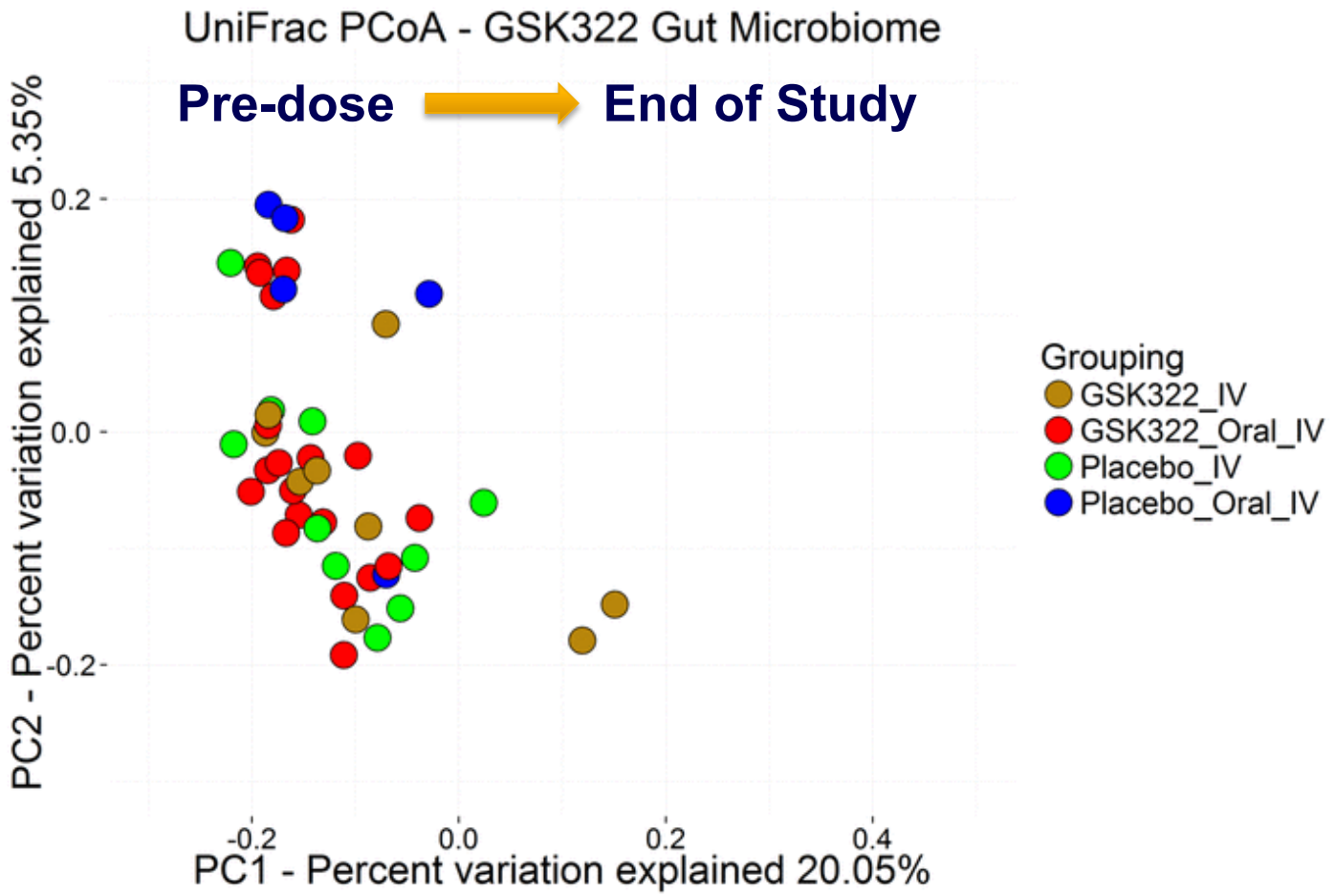
While bacterial species may vary in individuals, metabolic potential is conserved



Drug Effects on Overall Microbiota Diversity

Drug dosing method matters

- GSK'322, a novel first in-class antibiotic inhibits bacterial peptide deformylase
- Phase I dose escalation study in healthy volunteers
- ***Oral/IV*** dosing regimes notably changed the base-line microbiome while ***IV only drug dosing and placebo*** induced minimal change



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

Drug + Disease Associations with the Microbiome

Beyond antibiotics, other drugs impact microbiome communities

- Maier et al. 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. looked at gut microbiome associations with disease and medication in ~2700 UK Twin cohort:
  - Besides antibiotics and PPIs, anti-cholinergics, steroid inhalers, acetaminophens, SSRIs and opioids highly associated with microbiome changes
  - IBD, T2D, constipation, UTIs, food allergies, and 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

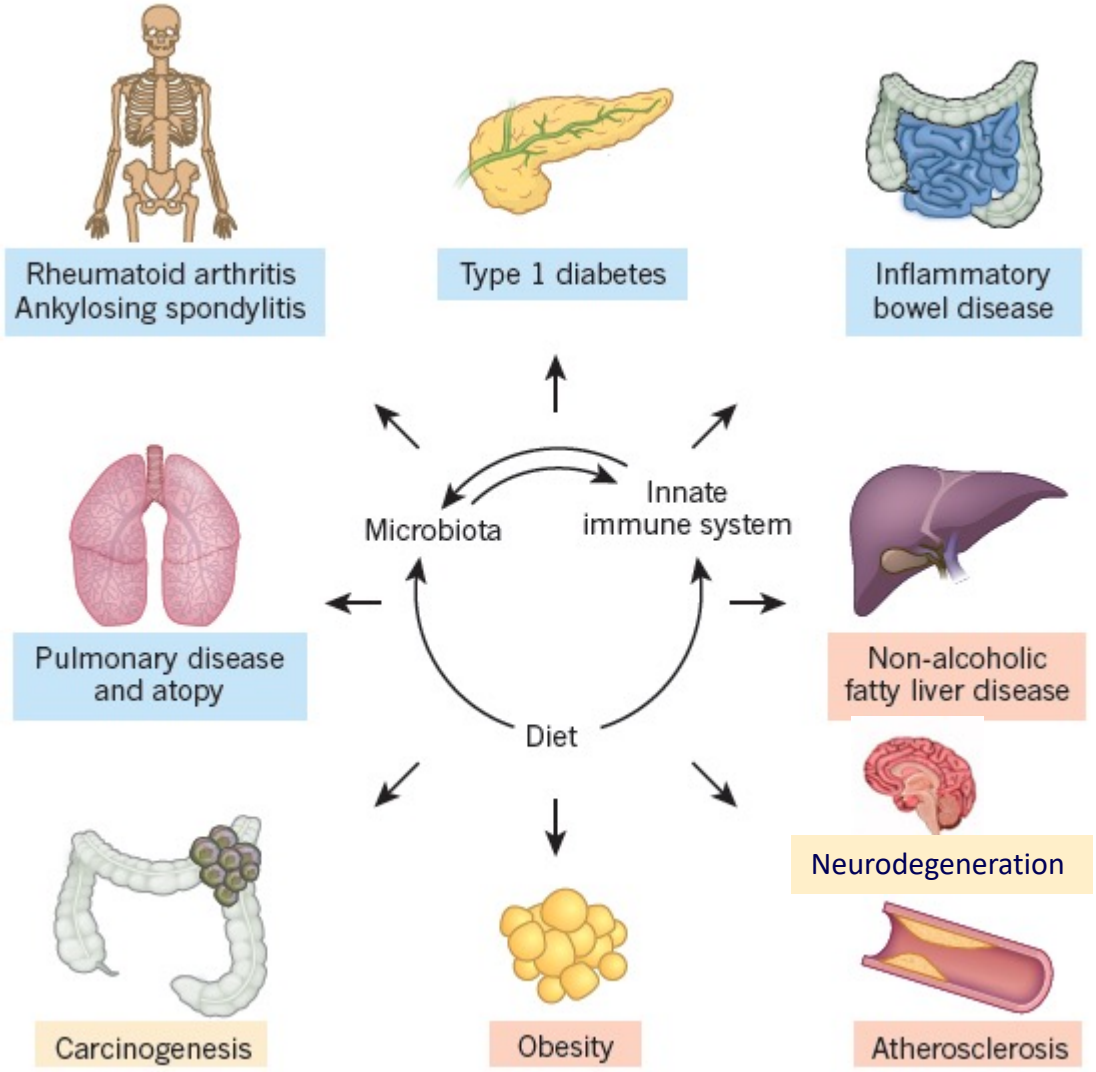
Matthew A. Jackson[1,2], Serena Verdi[1], Maria-Emanuela Maxan[3], Cheol Min Shin[1,4], Jonas Zierer[1,5], Ruth C.E. Bowyer[1], Tiphaine Martin[1,6], Frances M.K. Williams[1], Cristina Menni[1], Jordana T. Bell[1], Tim D. Spector[1] & Claire J. Steves[1,3]

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

Microbiome, Inflammation and Innate Immunity

Most diseases have an immuno-inflammation component

- Many inflammatory disorders are linked to dysbiosis of the microbiota
- Impacting immune and GI barrier functions
- Includes metabolic, neoplastic, neuro-degeneration, auto-immune and auto-inflammatory disorders
- Modulating the microbiome is a potential therapeutic strategy for multiple diseases



Thaiss et al. 2016 **Nature**. 535:65

Outline

1. Defining the “normal” vs “disease” microbiome

2. **Modulation of the microbiome in obesity/diabetes *in vivo* models**

3. Microbiome and clinical pharmacology

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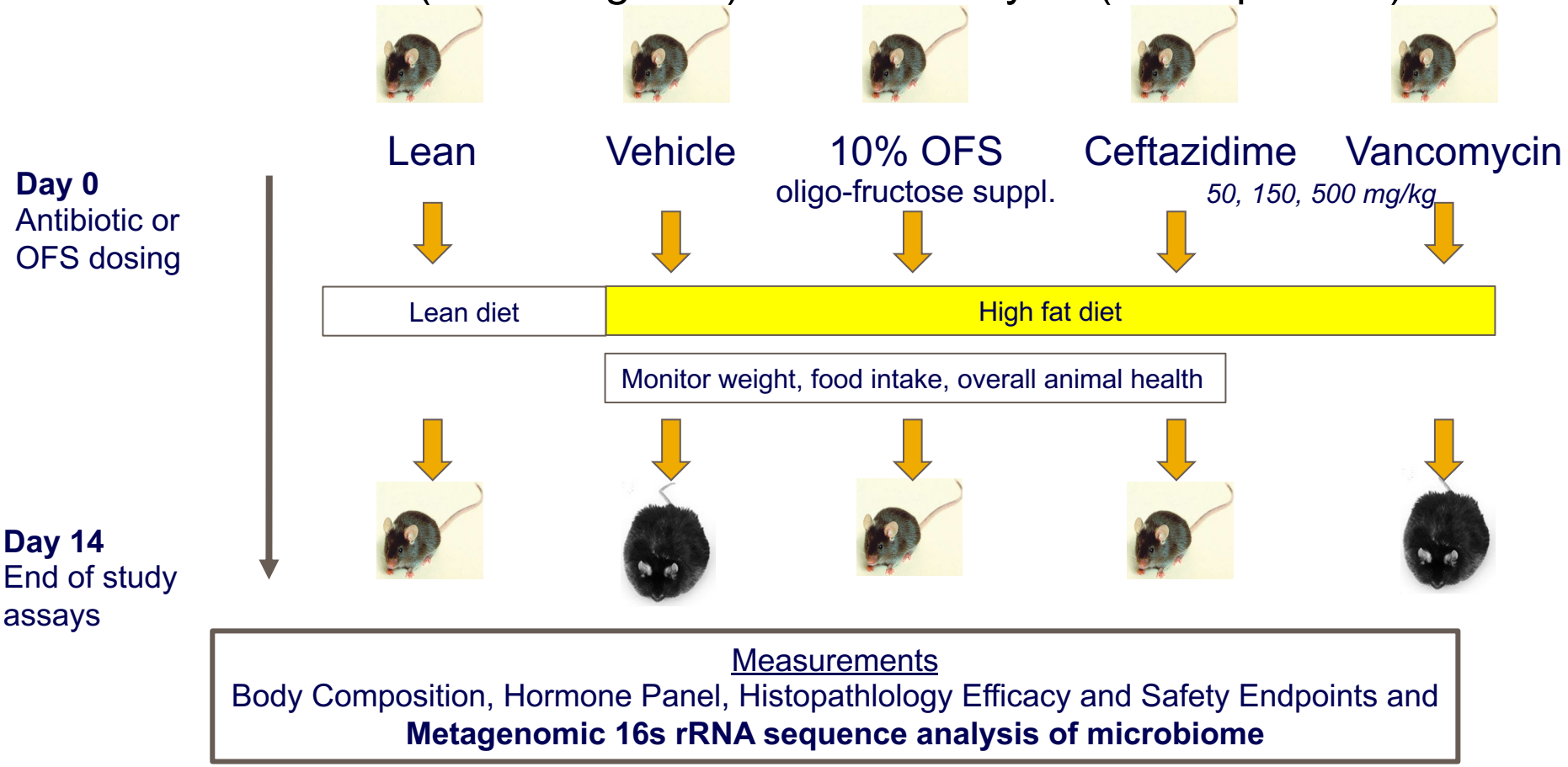
Antibiotic Modulation of Obesity and Diabetes

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)

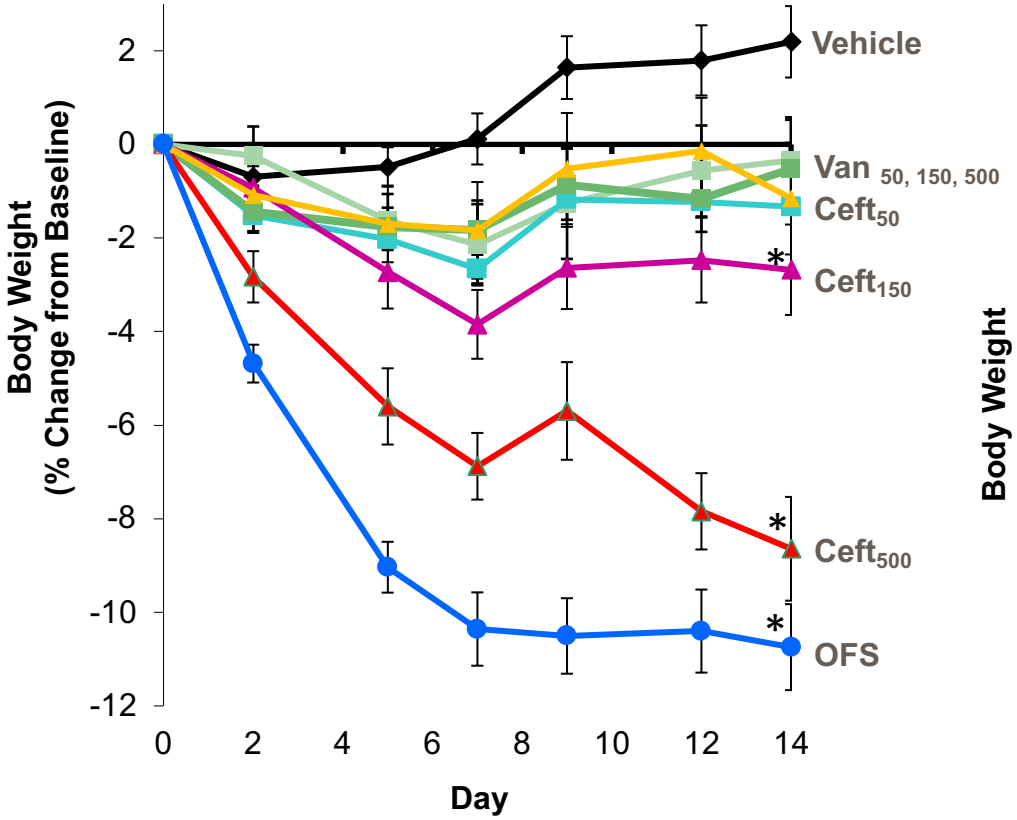


Rajpal et al. 2015. **PLoS One** 10:e0145499.

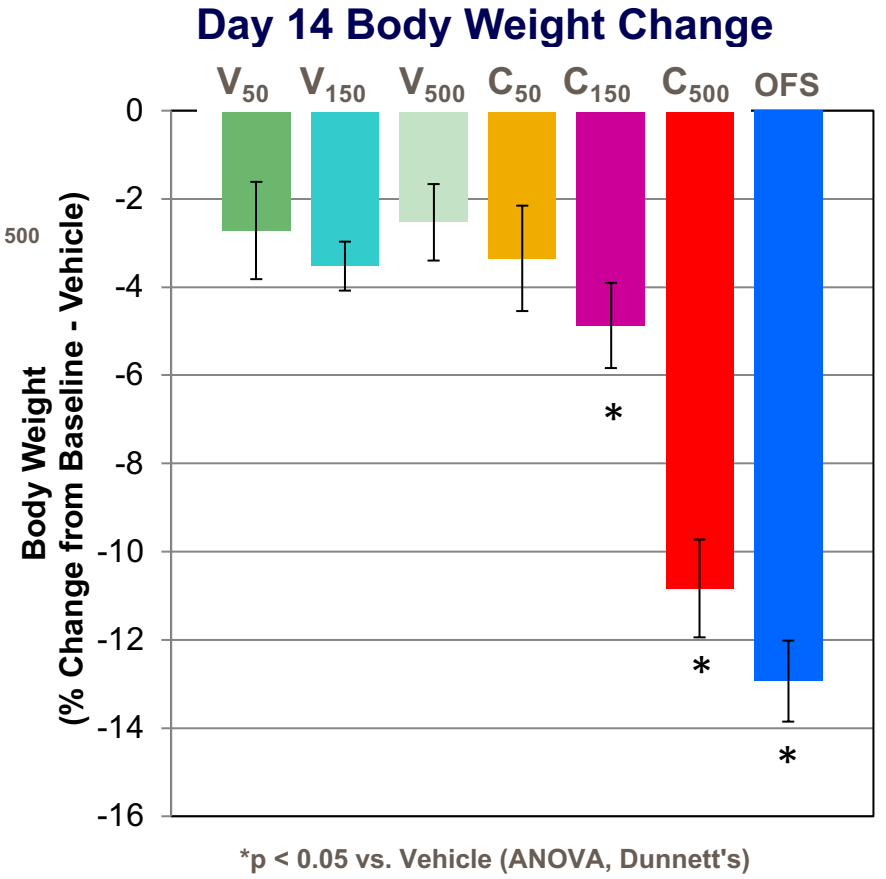
Differential Effects on Body Weight

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



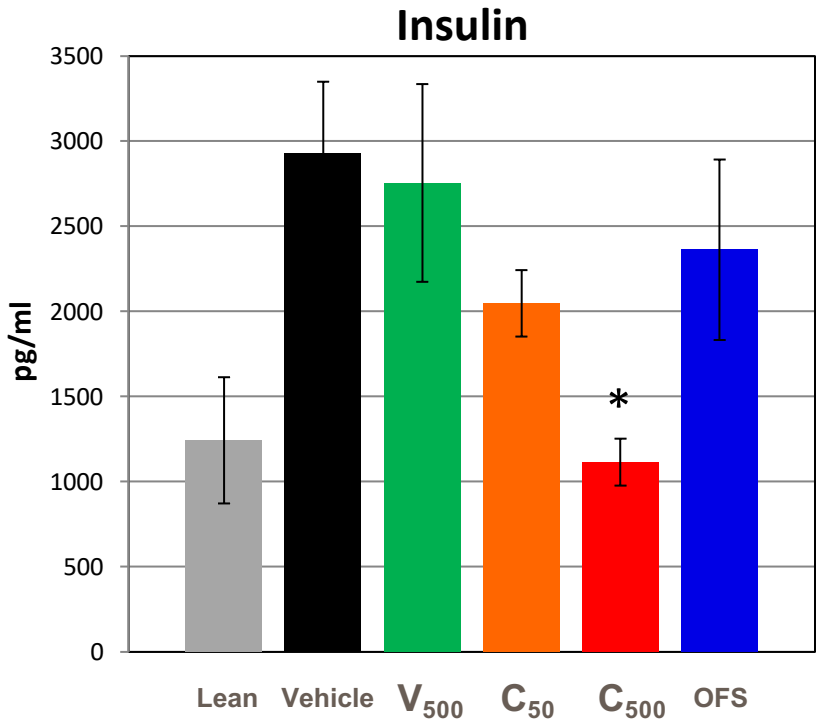
*p < 0.05 vs. Vehicle (ANOVA, Dunnett's)

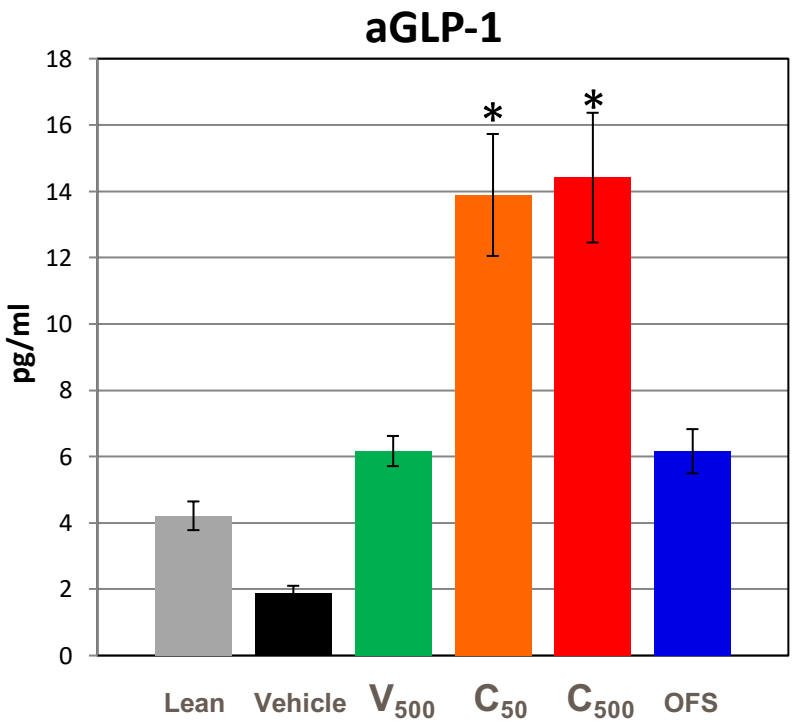
Rajpal et al. 2015. **PLoS One** 10:e0145499.

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

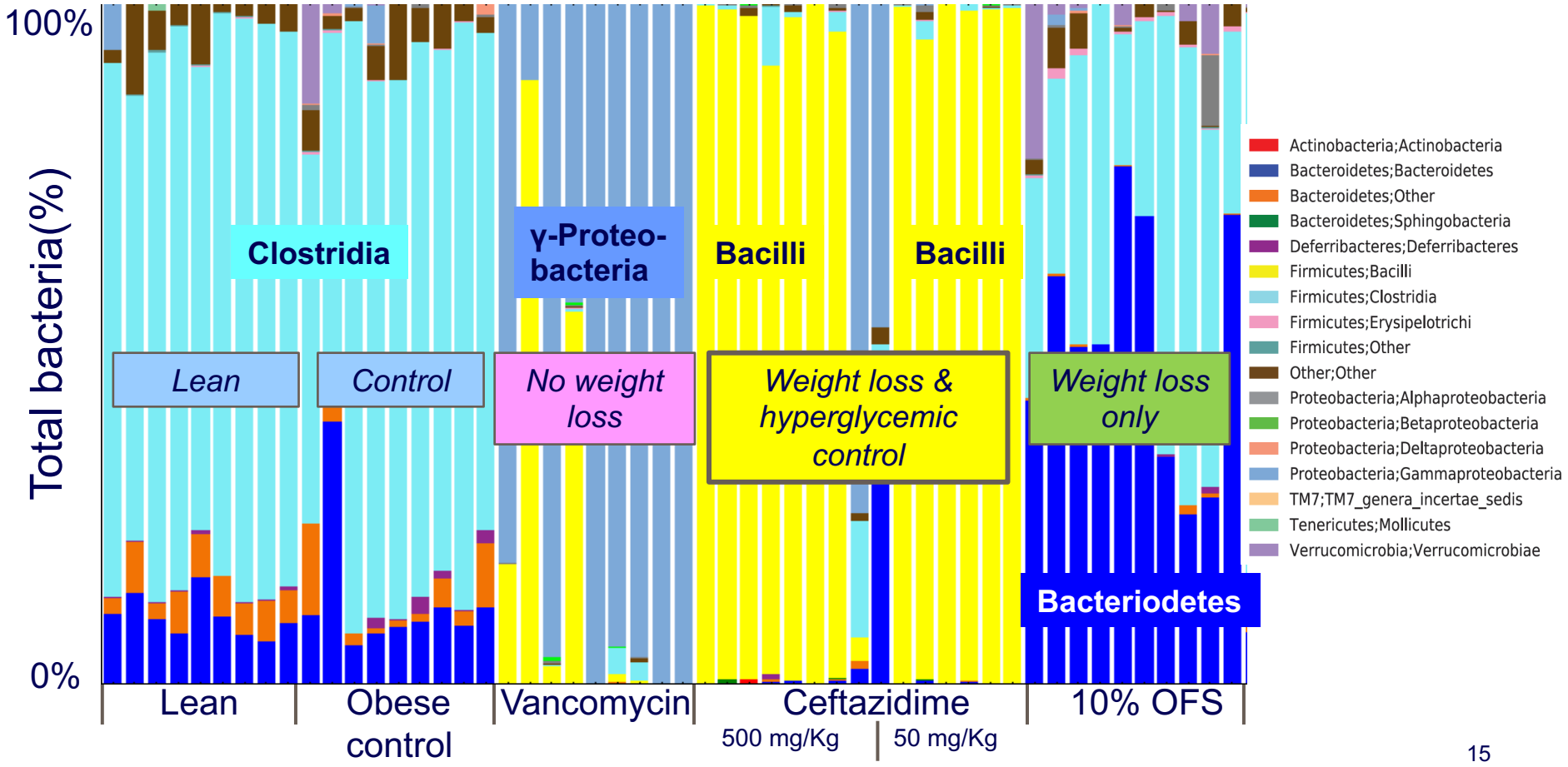




Distribution of Intestinal Bacterial Species

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



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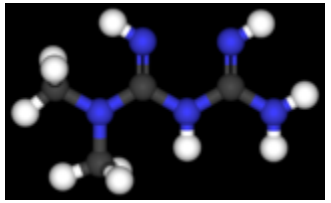
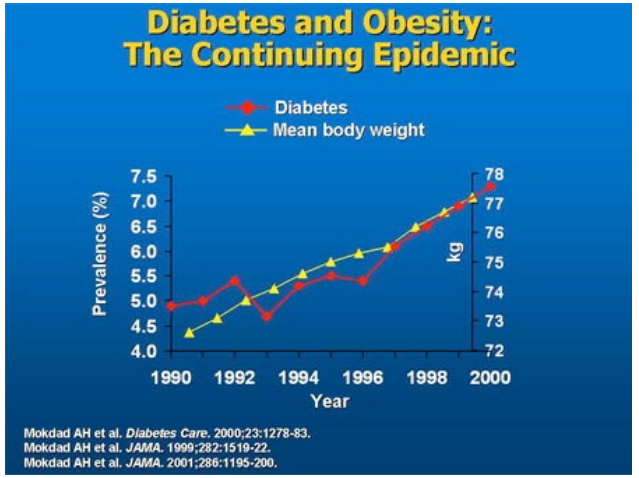
Gut Microbiome and Metformin Withdrawl

Understanding the gut pharmacology of widely used drugs

- Metformin is first-line drug of choice for the treatment of Type 2 diabetes mellitus (T2DM)



- Oral metformin decreases hepatic glucose production, but intravenous metformin is much less effective



- Gut-based pharmacology may be important for metformin action as an anti-diabetic medication

- The effects of metformin on gut bile acids, entero-endocrine hormones, and microbiome are not clear

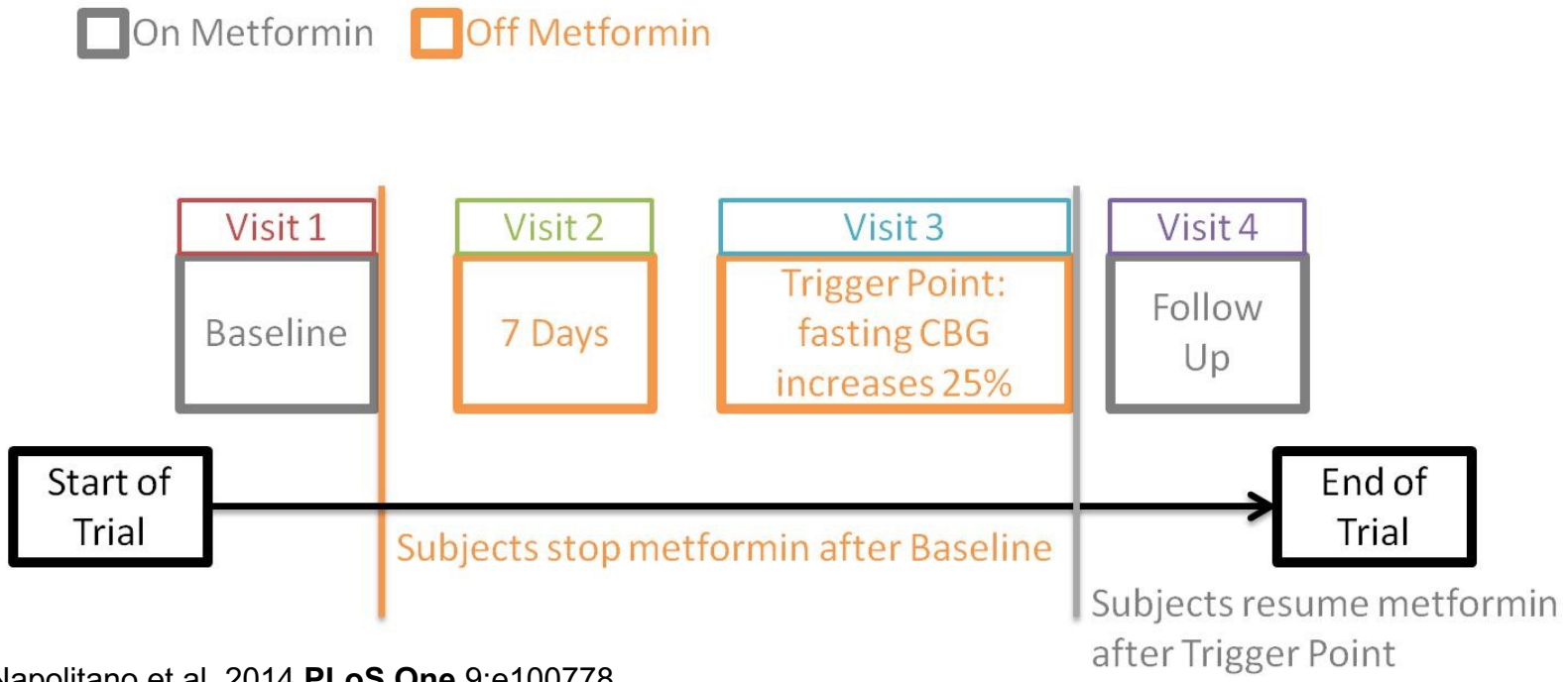
- **GSK study aim:** Evaluate T2DM patients “on” and “off” metformin to characterize the biochemical and microbiome responses

Napolitano et al. 2014 **PLoS One** 9:e100778

Gut Microbiome Metformin Study Design

T2DM subjects cycling through on-off-on metformin treatment

- 14 T2DM patients taken off metformin; Baseline measurements recorded
- When blood glucose reach 125% baseline, triggers metformin resumption
- Patients monitored daily until blood glucose levels return to baseline
- 4 fecal samples taken throughout study: 1) Baseline; 2) 7 days after metformin cessation; 3) metformin treatment resumes and 4) blood glucose returns to baseline

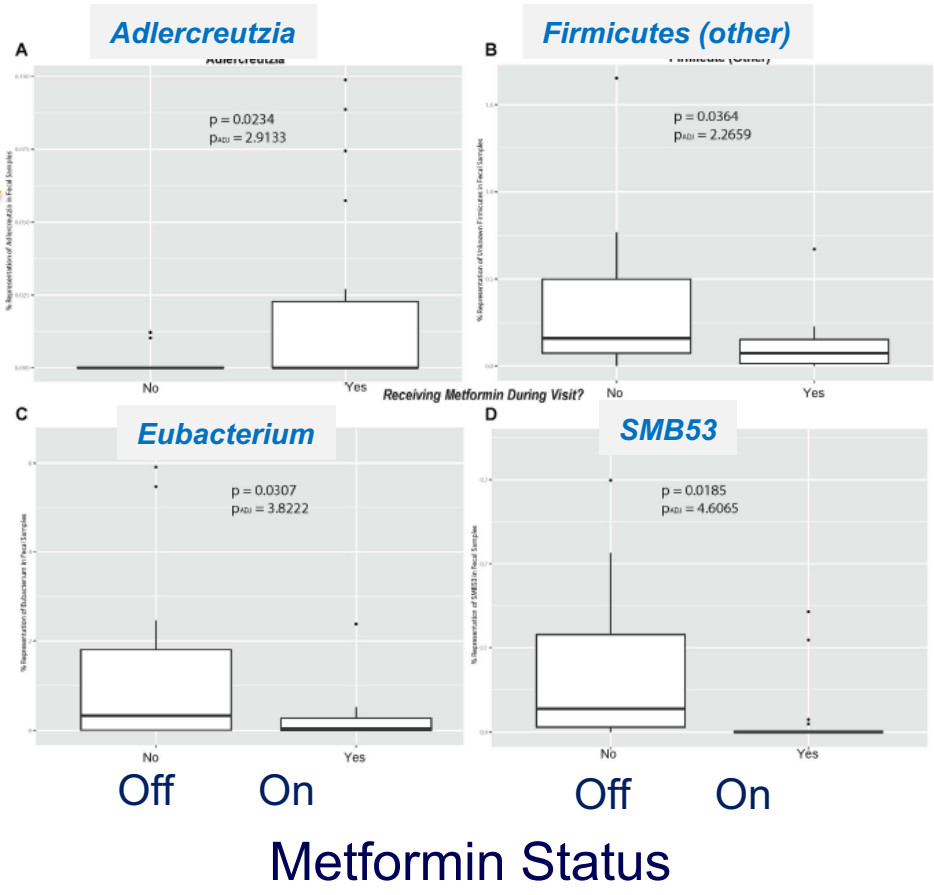


Napolitano et al. 2014 **PLoS One** 9:e100778

Novel Gut Pharmacology of Metformin

Microbiome manipulation could have a role in metformin MOA

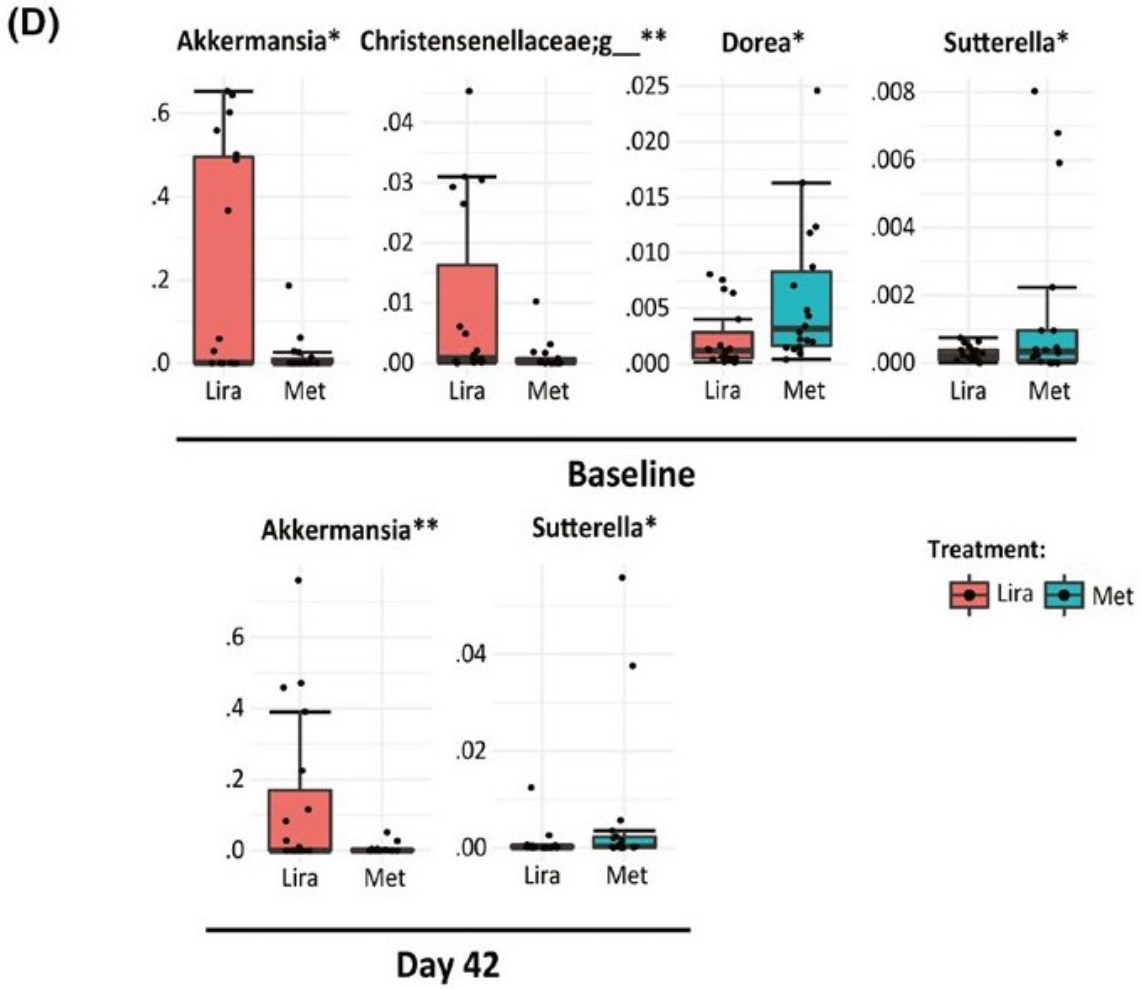
- Serum glucose and primary bile acids (Cholic acid) increase while off metformin
- *Adlercreutzia* sp., a known metabolizer of plant isoflavones (equol), was positively correlated with "on" metformin
- Equol regulates glucose uptake in adipocytes via PPAR-gamma insulin-stimulation pathways
- Dietary soybean isoflavones favorably affect metabolic phenotypes associated with T2DM
- Study suggests microbiome metabolism plays a role in metformin pharmacology in T2DM
  - Microbiome activity supported by other T2DM patient cohort studies



Napolitano et al. 2014 **PLoS One** 9:e100778

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

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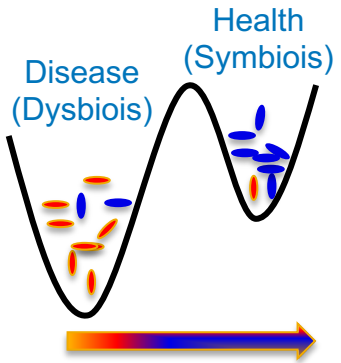
Overview of Microbiome Therapeutic Strategies

Targeting either the "messenger" or the "message"

Manipulate Microbial Ecology

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

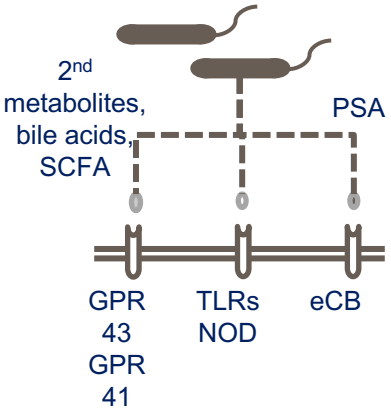


Rajpal & Brown 2013 **Drug Development Research** 74:376

Modulate Human-Microbe Crosstalk

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



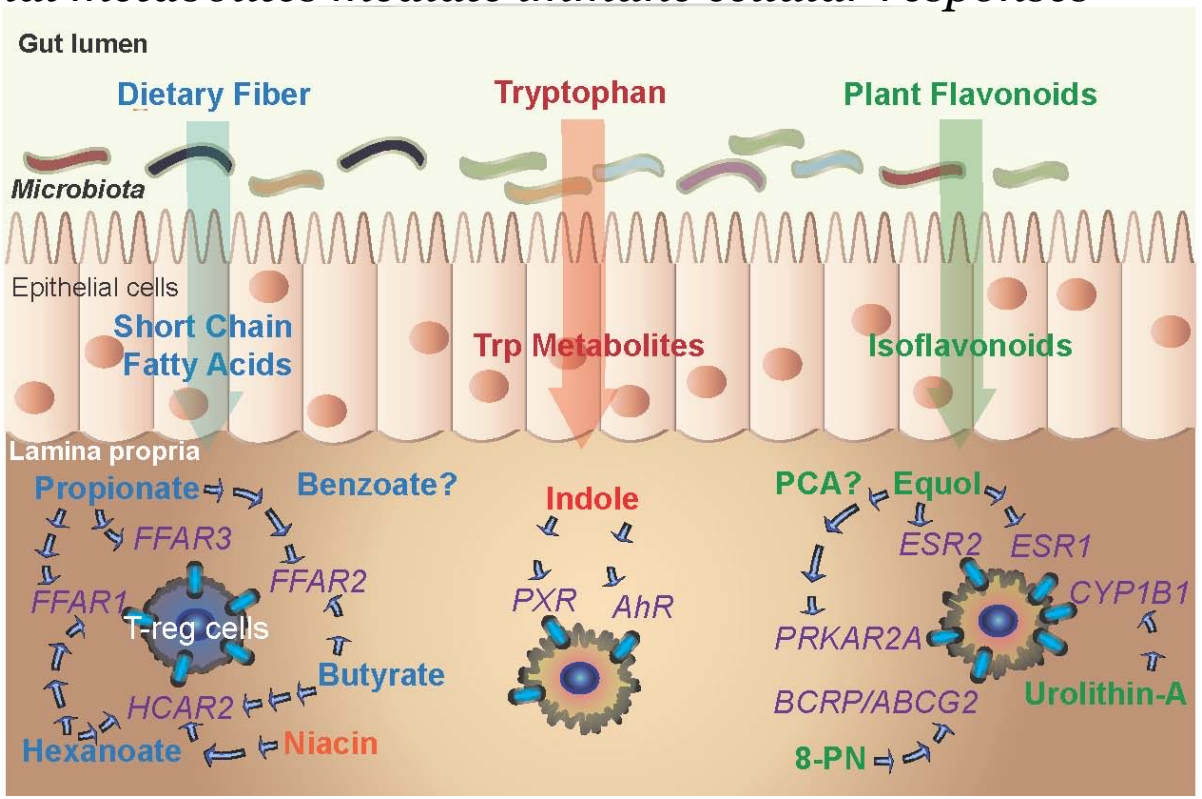
Challenges

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

Targeting Human Host-Microbial Crosstalk

Bacterial metabolites mediate immune cellular responses

Dr. Somdutta Saha, Early Talent PDF



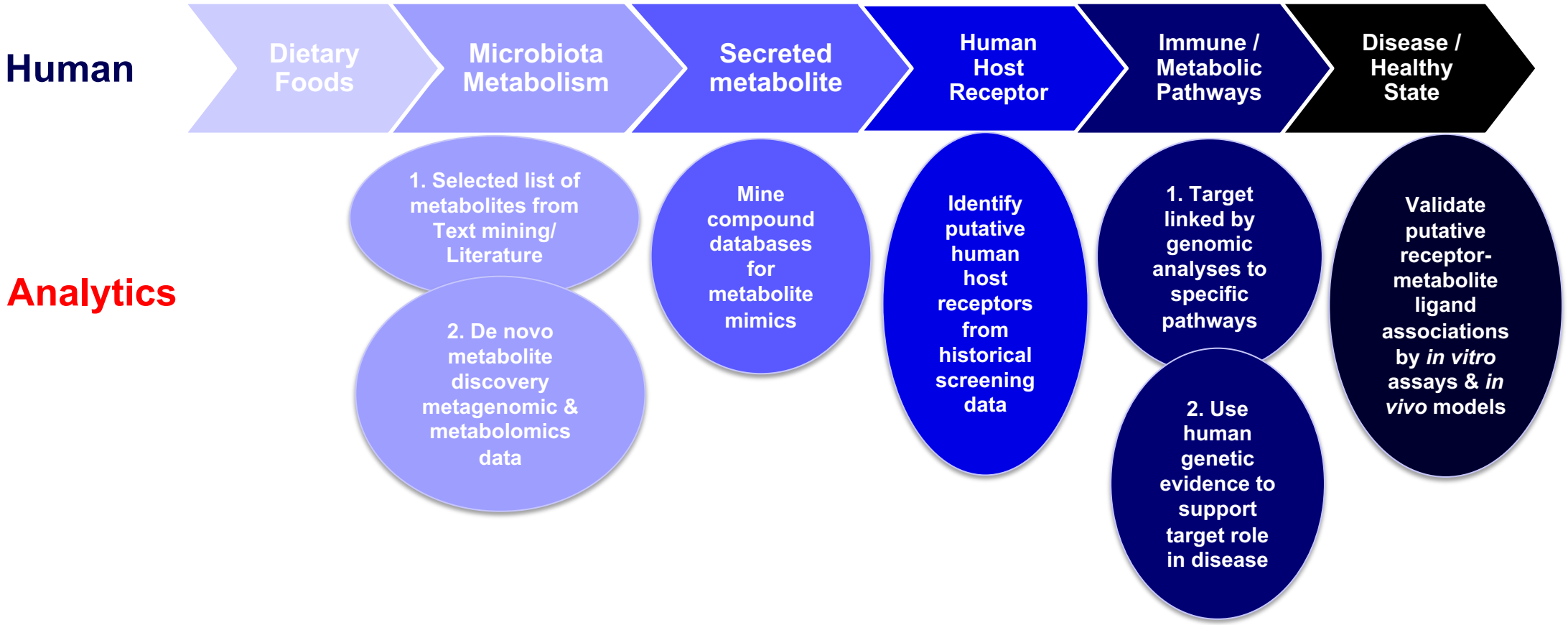
Saha et al. 2016. **Drug Discovery Today** 21:692

- 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)

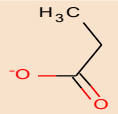
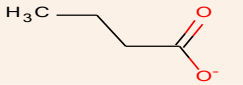
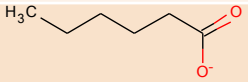
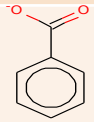
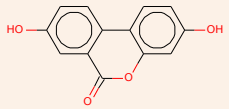
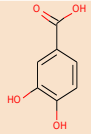
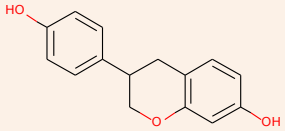
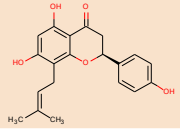
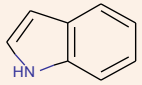
Searching For Bacterial Metabolite-Mimics

In silico approach to find metabolite compounds for optimization

- Pharma and public compound databases contain many natural and synthetic metabolite-like molecules, a subset of which have specific human target interaction data



Metabolites Reported As Immuno-modulators

Microbial Metabolite	Structure	Known Target (if any)
Propionate		G-protein coupled receptors
Butyrate		G-protein coupled receptors
Hexanoate		G-protein coupled receptors
Benzoate		Unknown
Niacin		G-protein coupled receptors
Urolithin -A		Cytochrome P450s family 1B1
Protocatechuic Acid (PCA)		Unknown
Equol		cAMP-protein kinase A Estrogen receptors
8-Prenylnaringenin (8-PN)		Unknown
Indole		Voltage Gated K+ channels

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SMILE String conversion

> 0.8 Tanimoto score

Search GSK 4.5 M compound collection

Retrieve metabolite-mimics

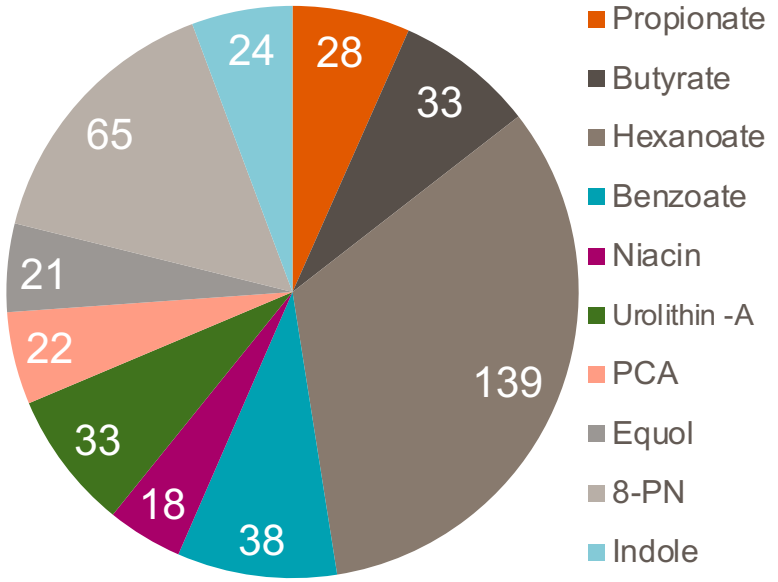
Retrieve any target assay data

List of microbial metabolites used in database searches, their 2D chemical structure and known targets (if any).

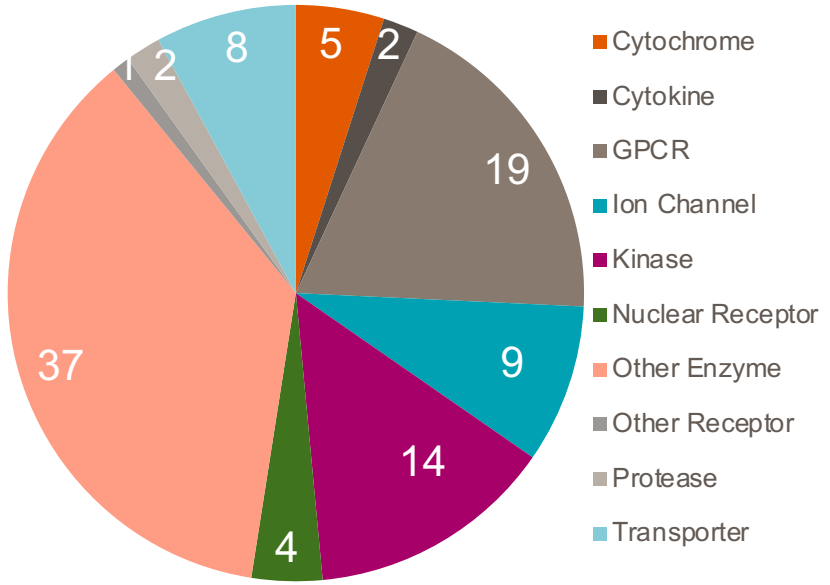
Metabolite-mimic Occurrences and Target Classes

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

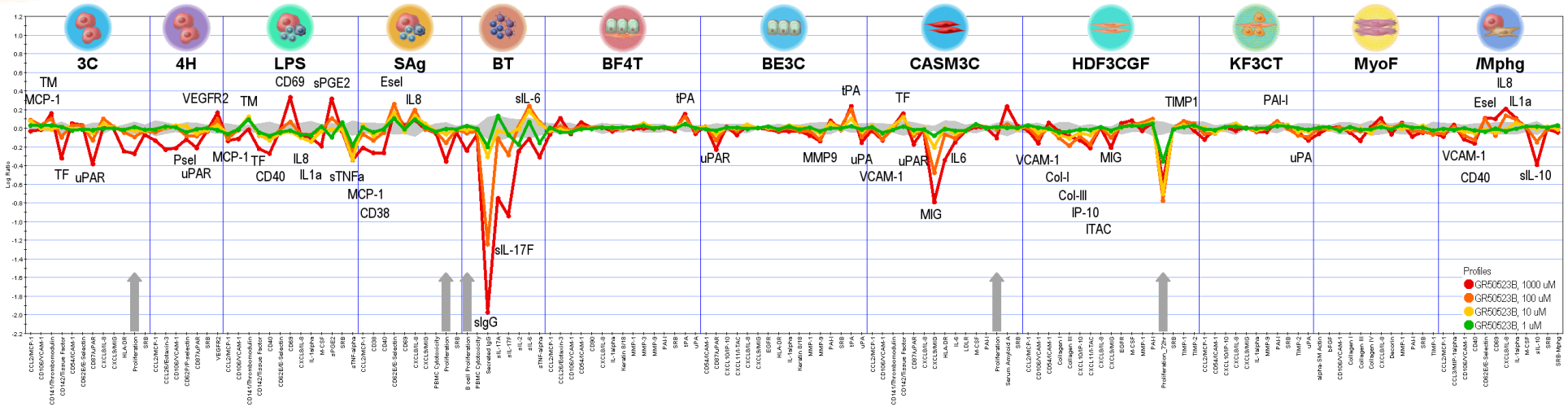
Both Known and Novel Targets Found

★ Metabolite and mimic progressed to DiscoveRx screen

Microbial Metabolite	Known Target (if any)	GSK Target Gene IDs Known and Novel
★ Propionate	G-protein coupled receptors like FFAR1(GPR40), FFAR3(GPR41), FFAR2 (GPR43)[5]	FFAR1, FFAR3, FFAR2
★ Butyrate	FFAR2(GPR43)[5], HCAR2 (GPR109A)[6], lysine-specific demethylases	KDM4A 4 genes
Hexanoate	G-protein coupled receptors[5]	FFAR4
★ Benzoate	Unknown	3 genes
Niacin	HCAR2 (GPR109A)[1]	HCAR2, 1 gene
★ Urolithin –A	CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1)[6]	CYP1A2, 3 genes
Protocatechuic Acid (PCA)	Unknown	3 genes
★ Equol	PRKAR2A (cAMP-protein kinase A)[7], estrogen receptors (ERs)-ESR1 (Erα) and ESR2 (Erβ)[8]	ESR1, ESR2, 2 genes
8-Prenylnaringenin (8-PN) ★	Unknown	3 genes
Indole	Voltage Gated K+ channels[9]	3 genes

BioMAP: Profiling Metabolite Cellular Phenotypes

DiscoveRx
Simple Solutions for Complex Biology



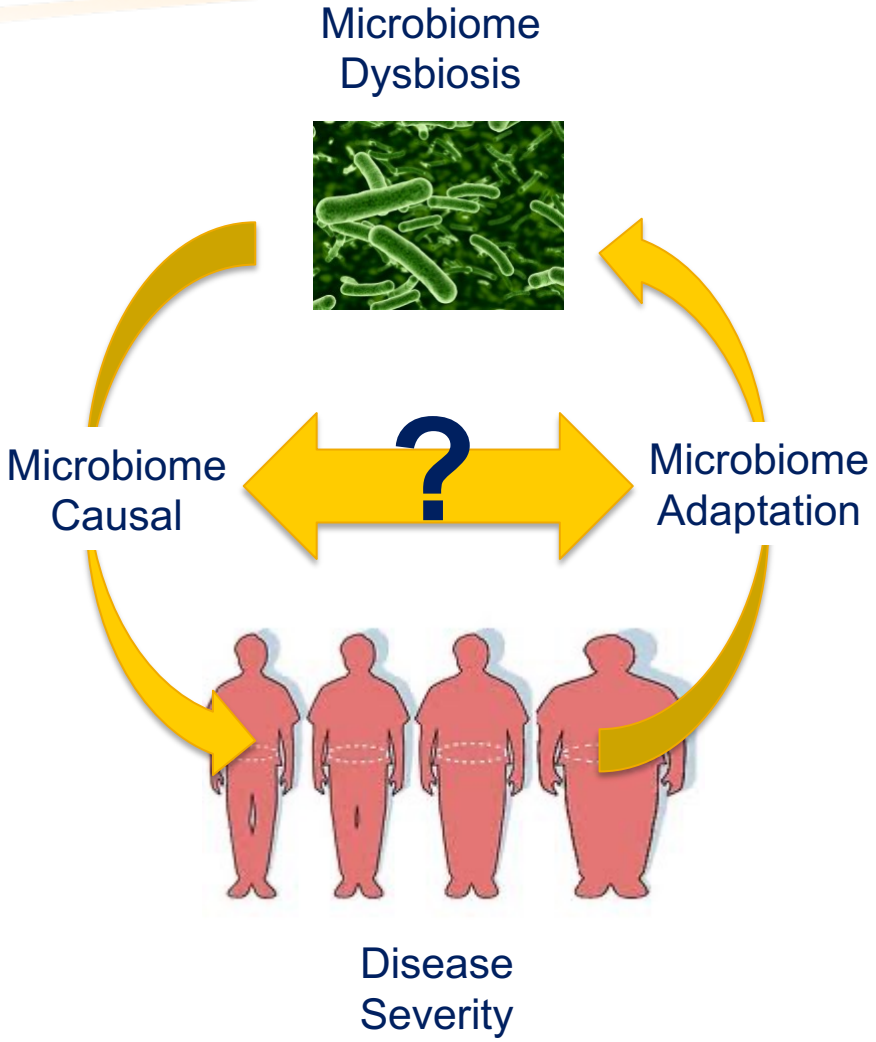
Disease Relevance	CV, Chronic inflammation	Asthma, Allergy, Oncology, Autoimmunity	CV, Chronic inflammation	Fibrosis Chronic inflammation	CV, Chronic inflammation

- **Example metabolite-mimic profile (butyrate) across primary cell assays:**
  - Modulators of endothelial cells, T cells, B cells
  - Inflammation-related activity – modulation of P-selectin, sTNFα, VCAM-1, MIG, IL-6, IP-10, etc.
  - Immunomodulatory activities – modulation of CD40, CD38, sIgG, and cytokines
  - Tissue remodeling activities – modulation of MMP-9, Collagen, etc.

GSK unpublished data

Challenge: Microbiome-to-Disease Causality?

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



- Are changes in the microbiome causing disease or merely adaptations to the disease environment?
- How do microbiome changes affect disease mechanisms?
- 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.

Computational Biologist – Host-Microbe Immunity

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  - Requisition ID: WD181298
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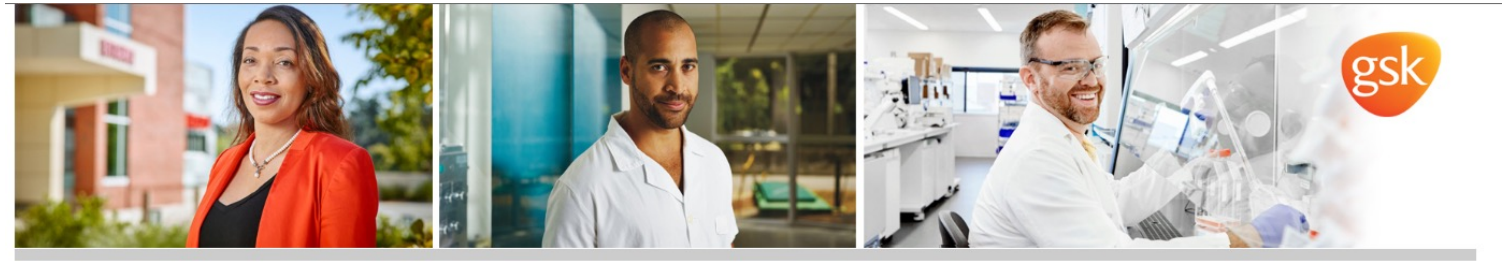

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