The Human Microbiome: a New Frontier in Health

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Department of Medicine
University of California San Francisco

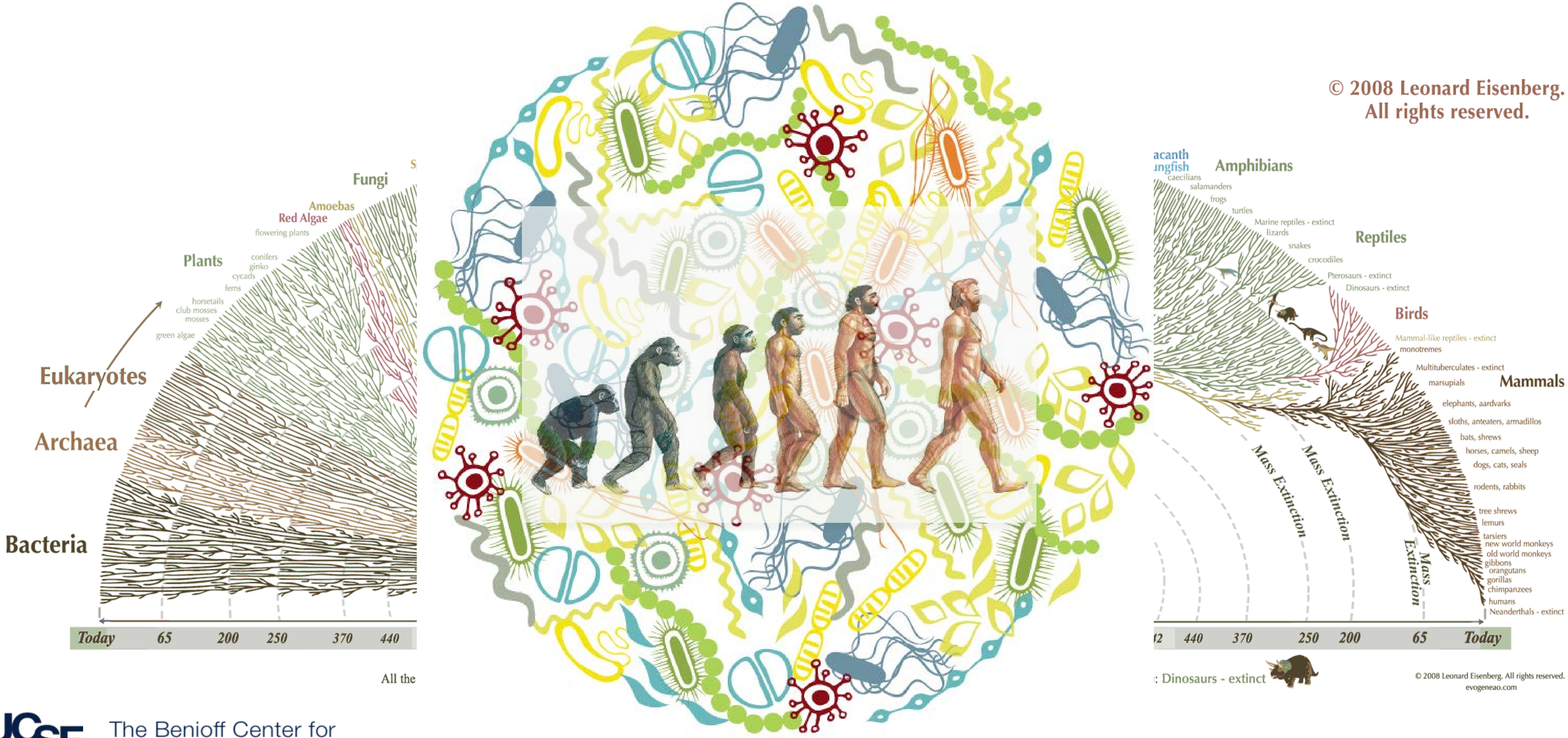
UCSF The Benioff Center for Microbiome Medicine

https://microbiome.ucsf.edu

What We'll Cover Tonight…..

- How do you study entire populations of microbes?
- Human microbiome 101!
- Case study – leveraging the early life gut microbiome to predict and treat childhood allergic asthma
- What's next?

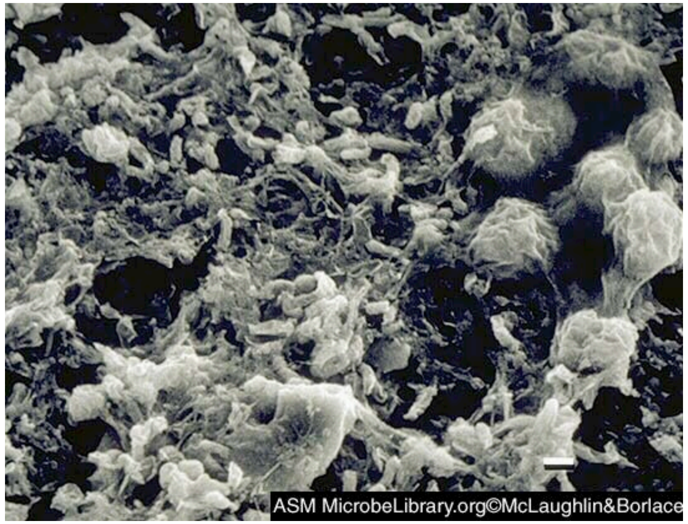
Microbes Pre-date Earth’s Biodiversity



Tree of life – Leonard Eisenberg

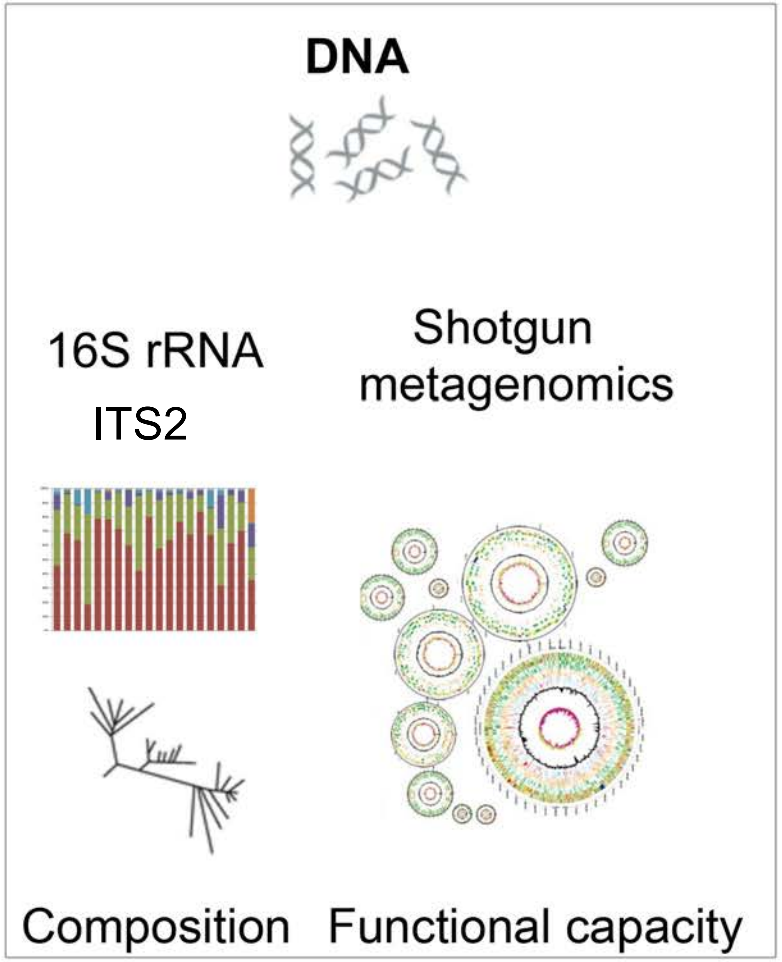
Culture-based Approaches do not Reflect the True Diversity or Physiology of Microorganisms

≠



ASM MicrobeLibrary.org©McLaughlin&Borlace

Enabling Tools to Interrogate Microbial Dark Matter



Next-generation sequencing platforms

nature microbiology

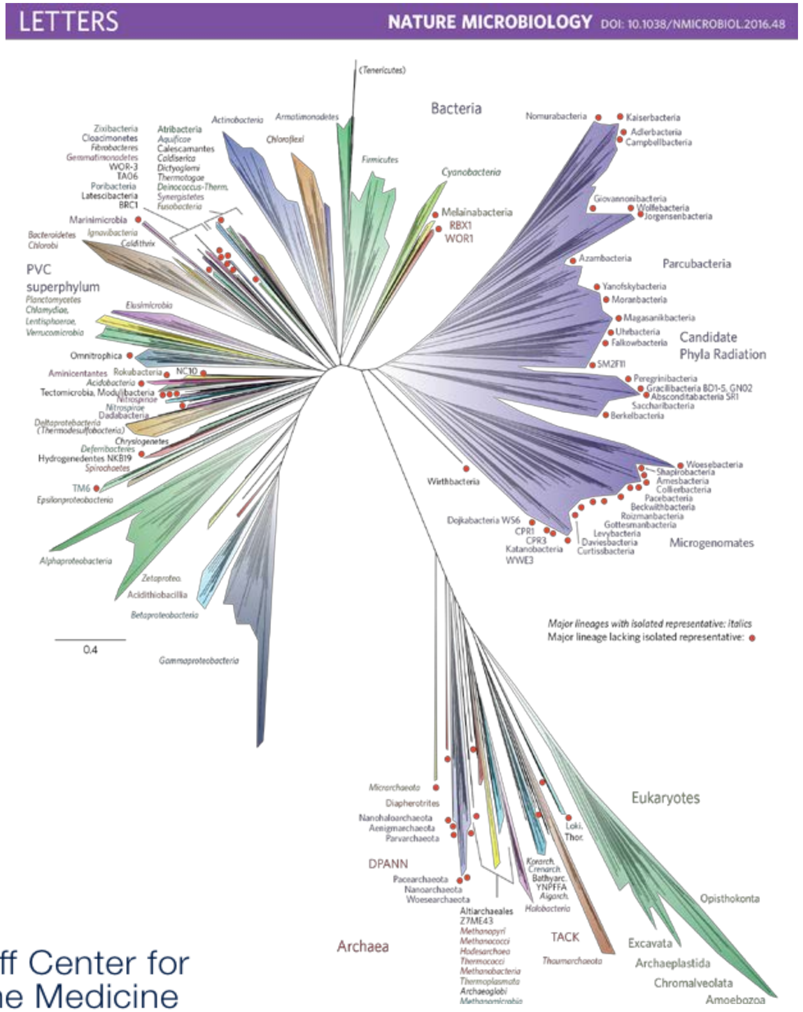
LETTERS

PUBLISHED: 11 APRIL 2016 | ARTICLE NUMBER: 16048 | DOI: 10.1038/NMICROBIOL.2016.48

OPEN

A new view of the tree of life

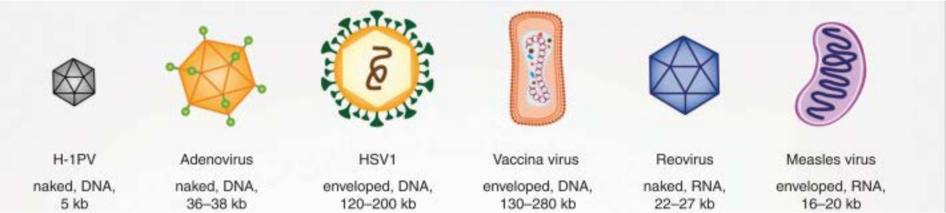
Laura A. Hug[1†], Brett J. Baker[2], Karthik Anantharaman[1], Christopher T. Brown[3], Alexander J. Probst[1], Cindy J. Castelle[1], Cristina N. Butterfield[1], Alex W. Hernsdorf[3], Yuki Amano[4], Kotaro Ise[4], Yohey Suzuki[5], Natasha Dudek[6], David A. Relman[7,8], Kari M. Finstad[9], Ronald Amundson[9], Brian C. Thomas[1] and Jillian F. Banfield[1,9*]

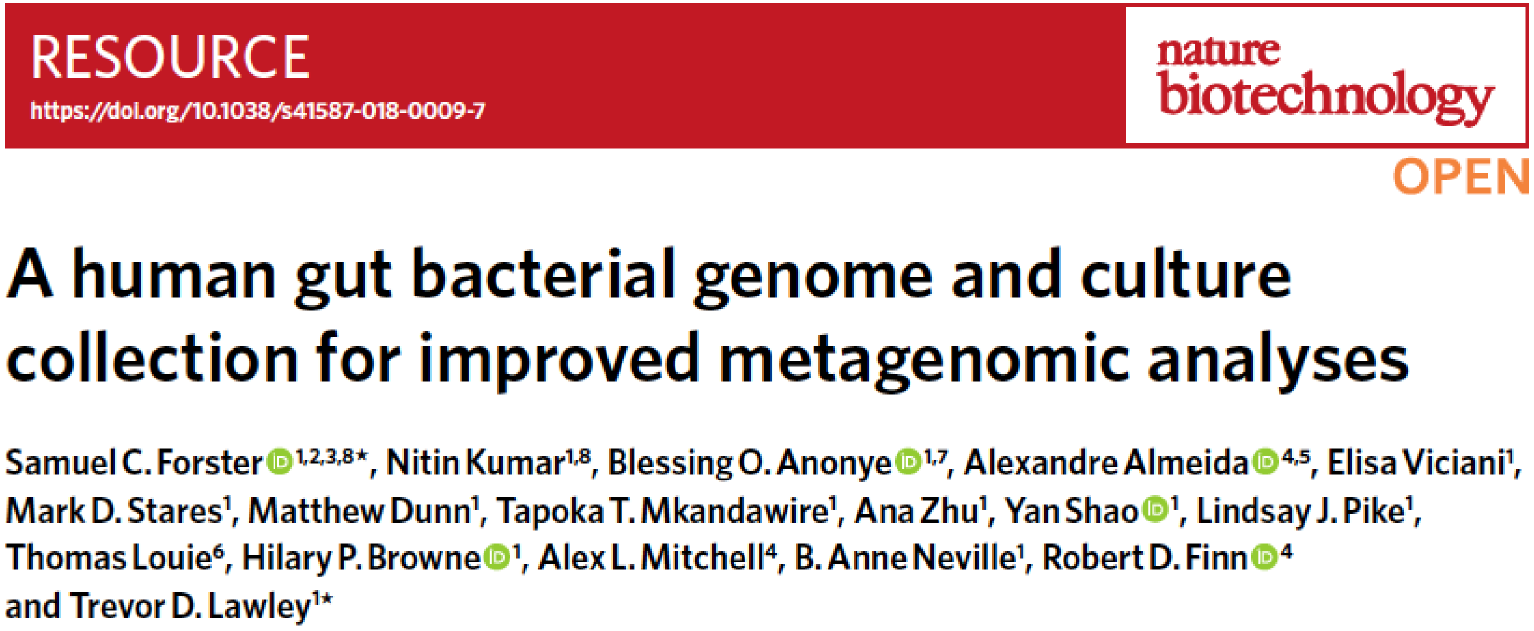


LETTERS NATURE MICROBIOLOGY DOI: 10.1038/NMICROBIOL.2016.48

Fungi

Viruses





RESOURCE
https://doi.org/10.1038/s41587-018-0009-7
nature biotechnology
OPEN

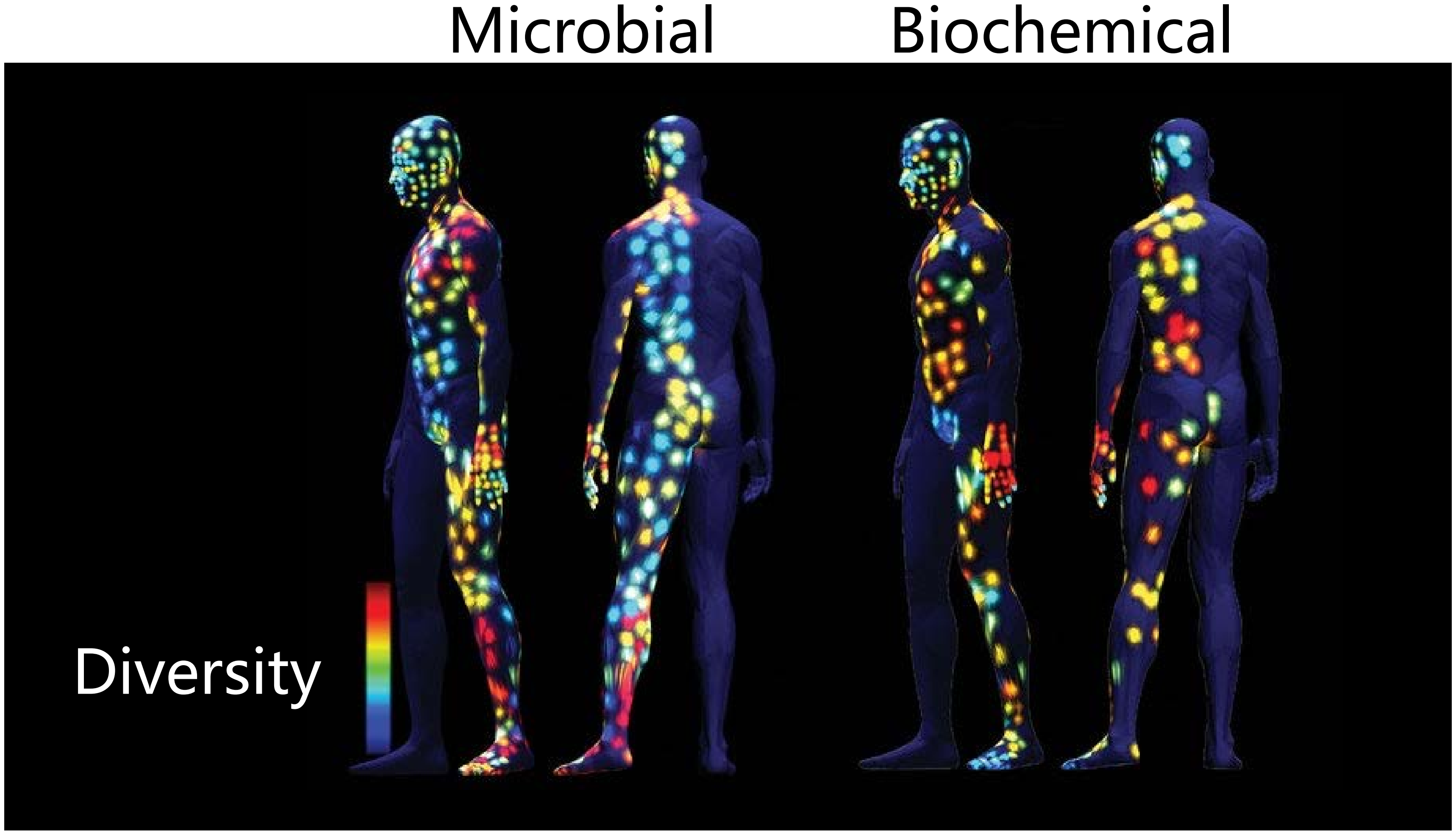
A human gut bacterial genome and culture collection for improved metagenomic analyses

Samuel C. Forster[1,2,3,8]*, Nitin Kumar[1,8], Blessing O. Anonye[1,7], Alexandre Almeida[4,5], Elisa Viciani[1], Mark D. Stares[1], Matthew Dunn[1], Tapoka T. Mkandawire[1], Ana Zhu[1], Yan Shao[1], Lindsay J. Pike[1], Thomas Louie[6], Hilary P. Browne[1], Alex L. Mitchell[4], B. Anne Neville[1], Robert D. Finn[4] and Trevor D. Lawley[1]*

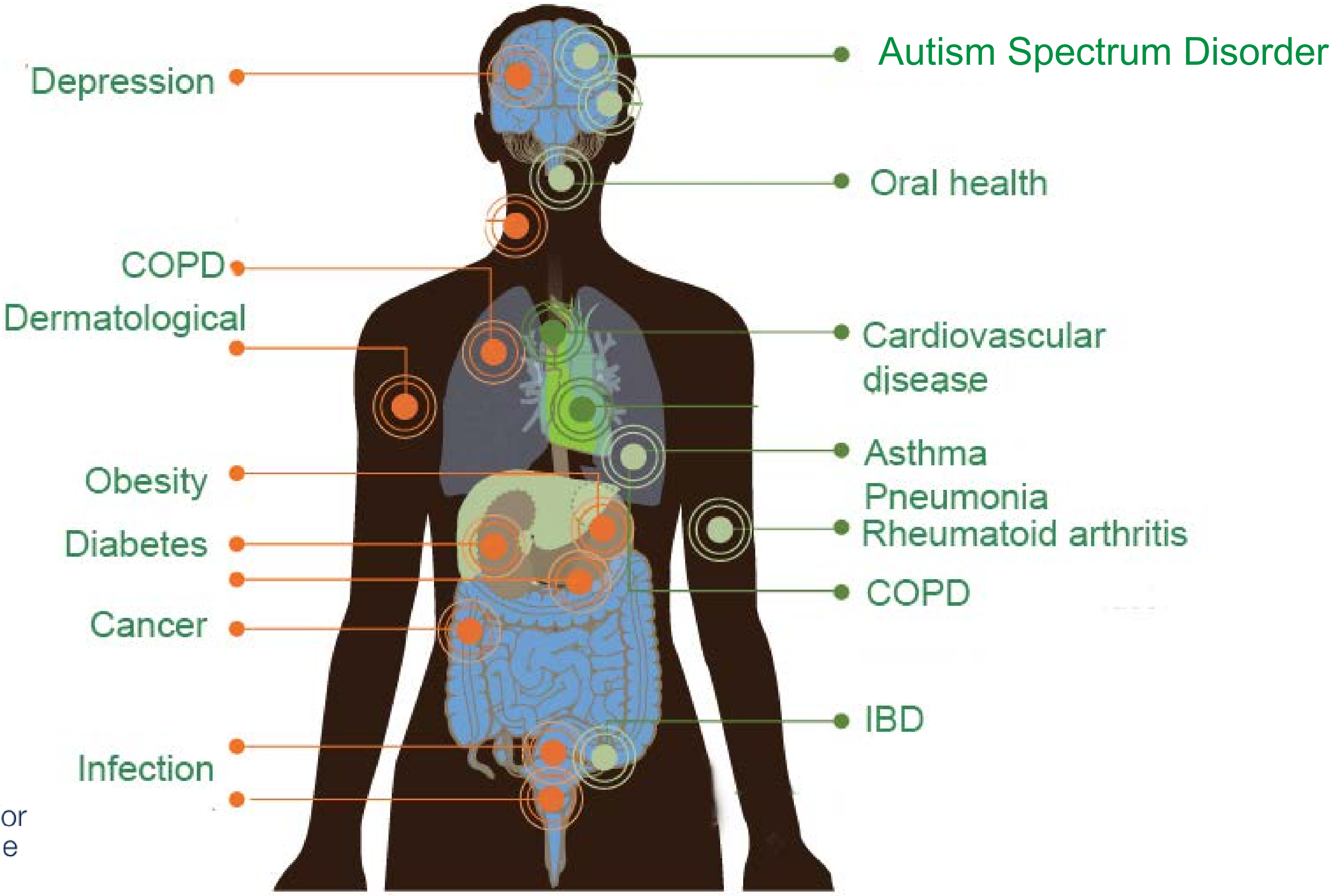
- Human Gastrointestinal Bacteria Culture Collection (HBC)
- Set of 737 whole-genome-sequenced bacterial isolates
    - 273 species (105 novel species)
    - 31 families in the human gastrointestinal microbiota

Nature Biotechnology | VOL 37 | 186 FEBRUARY 2019 | 186–192

Humans are Superorganisms



MICROBIOME PERTURBATION ASSOCIATES WITH DISEASE



Depression

COPD

Dermatological

Obesity

Diabetes

Cancer

Infection

Autism Spectrum Disorder

Oral health

Cardiovascular disease

Asthma

Pneumonia

Rheumatoid arthritis

COPD

IBD

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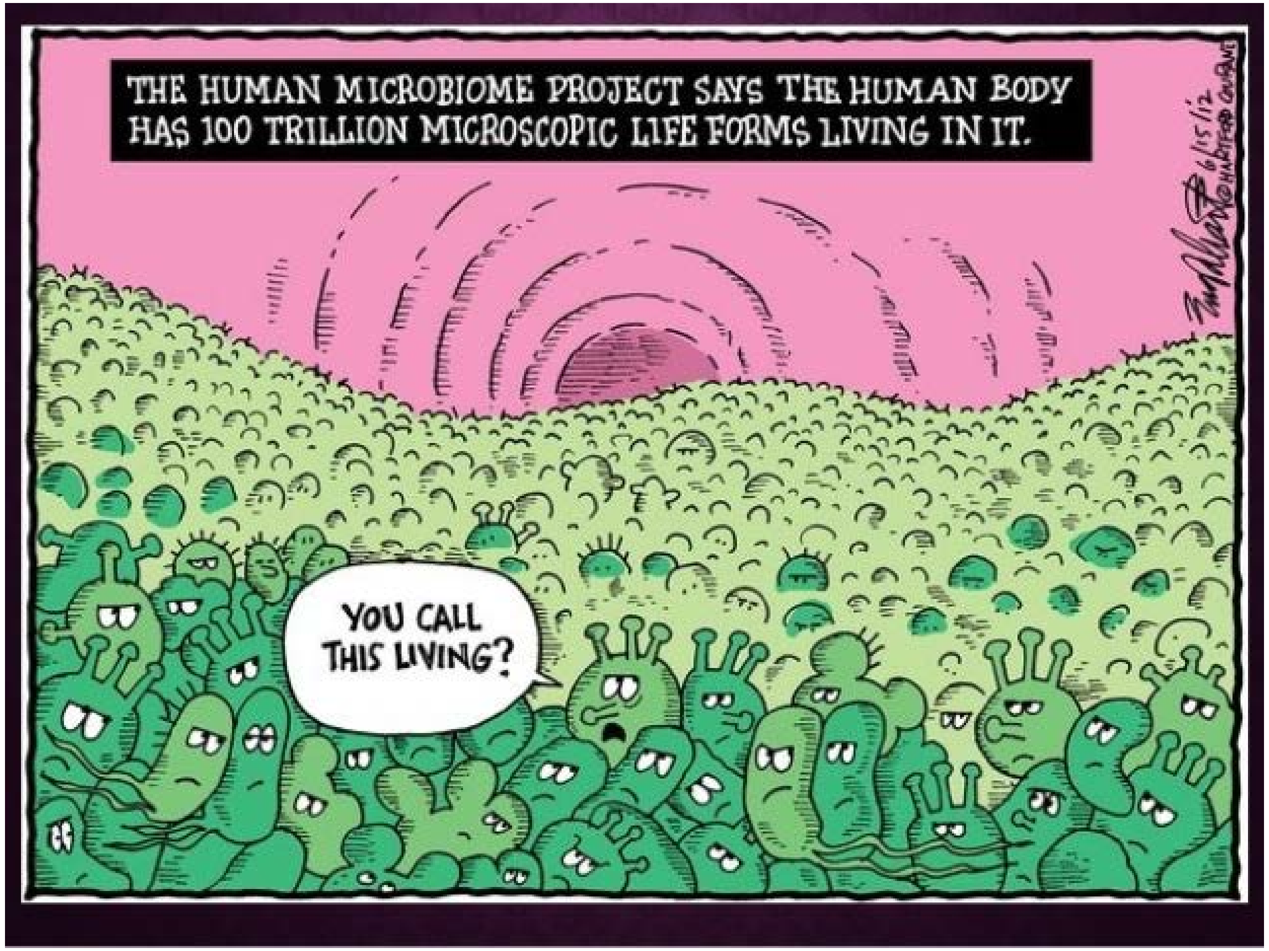
Microbiome Medicine

The Gut Microbiome is Home to Several Trillion Microbes



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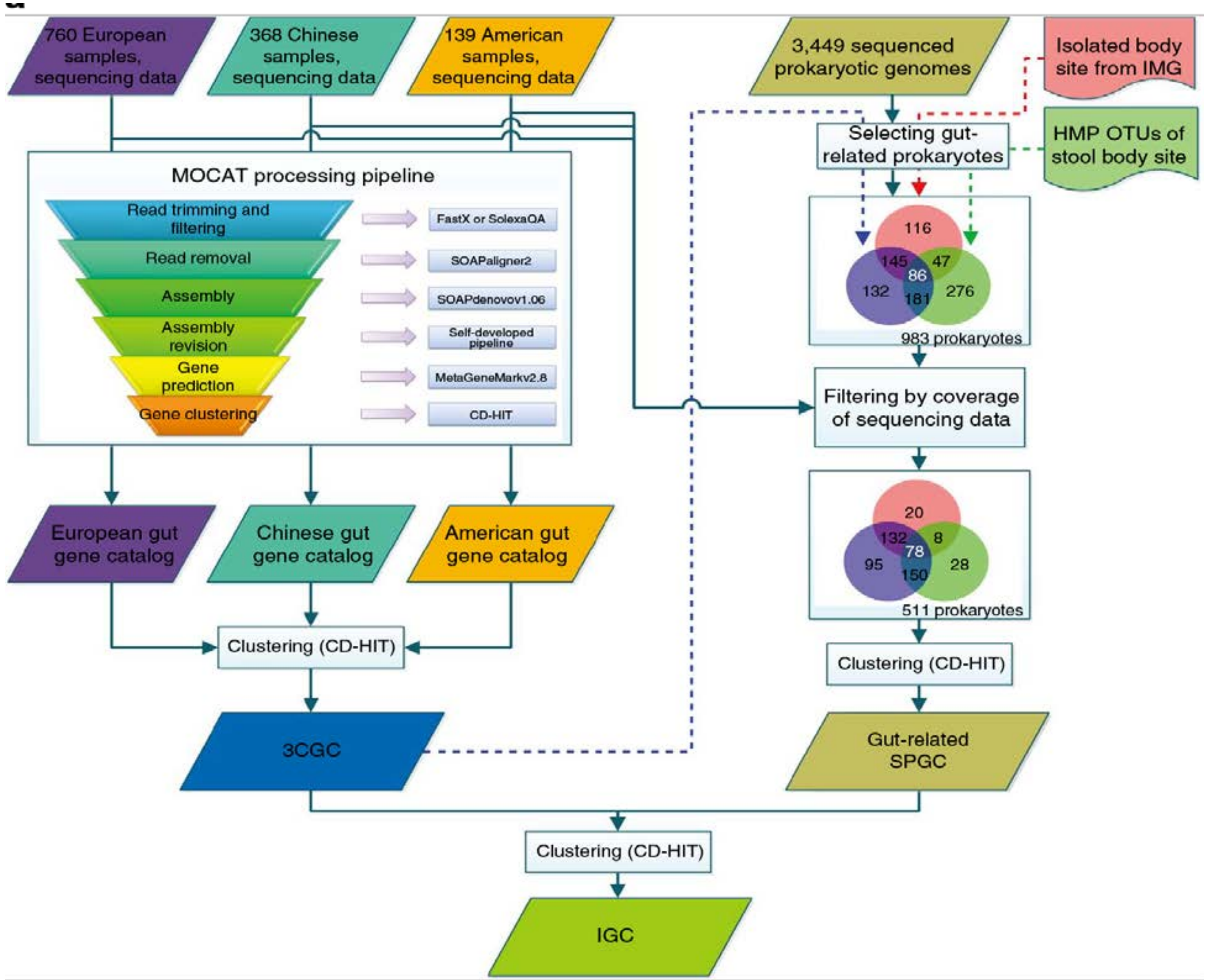
Genetic Capacity of the Gut Microbiome Dwarfs that of the Human Host



nature biotechnology

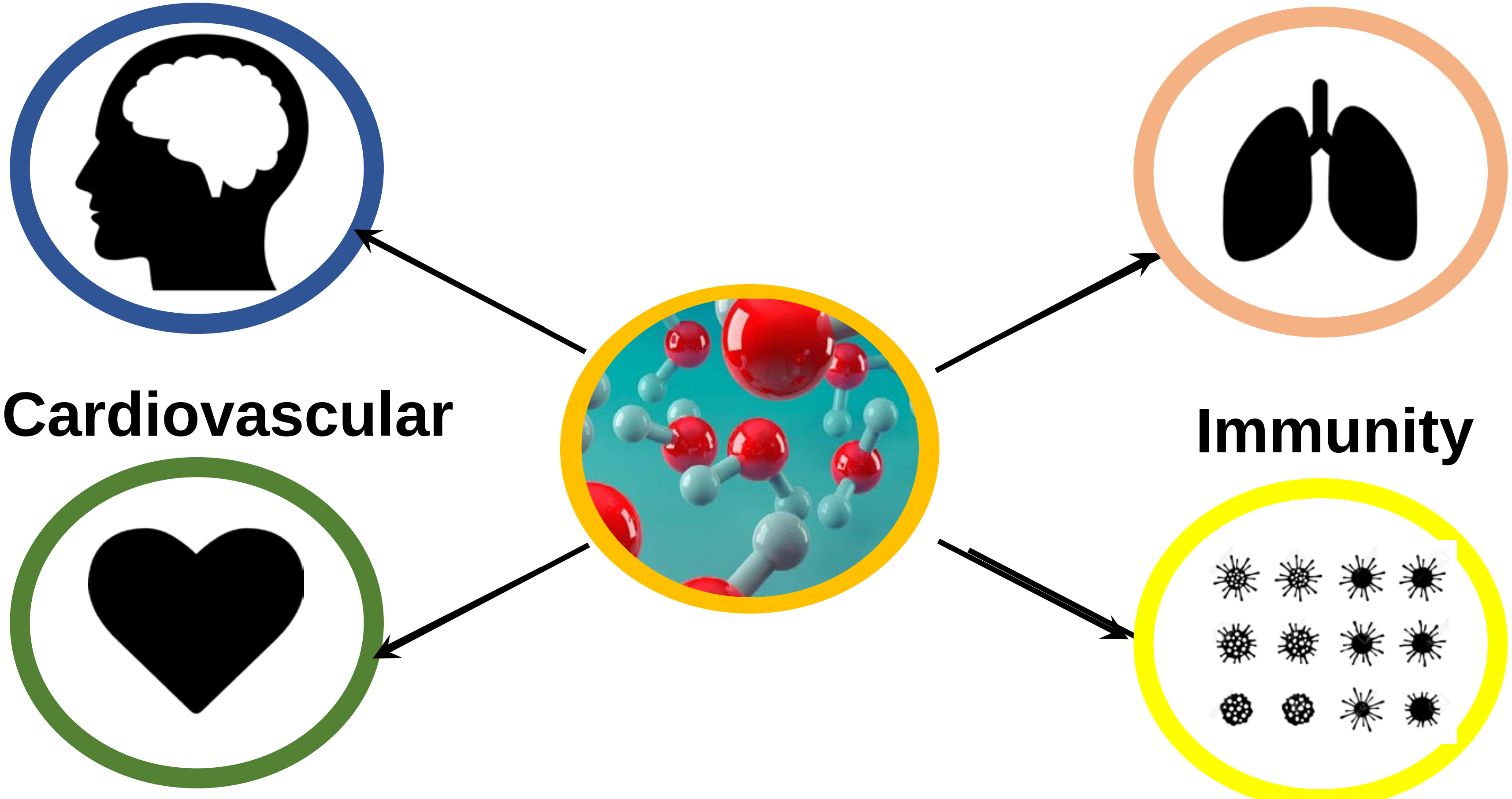
An integrated catalog of reference genes in the human gut microbiome

Junhua Li[1–3,19], Huijue Jia[1,19], Xianghang Cai[1,19], Huanzi Zhong[1,19], Qiang Feng[1,4,19], Shinichi Sunagawa[5], Manimozhiyan Arumugam[1,5,6], Jens Roat Kultima[5], Edi Prifti[7], Trine Nielsen[6], Agnieszka Sierakowska Juncker[8], Chaysavanh Manichanh[9], Bing Chen[1], Wenwei Zhang[1], Florence Levenez[7], Juan Wang[1], Xun Xu[1], Liang Xiao[1], Suisha Liang[1], Dongya Zhang[1], Zhaoxi Zhang[1], Weineng Chen[1], Hailong Zhao[1], Jumana Yousuf Al-Aama[10,11], Sherif Edris[11,12], Huanming Yang[1,11,13], Jian Wang[1,13], Torben Hansen[6], Henrik Bjørn Nielsen[8], Søren Brunak[8], Karsten Kristiansen[4], Francisco Guarner[9], Oluf Pedersen[6], Joel Doré[7,14], S Dusko Ehrlich[7,15], MetaHIT Consortium[16], Peer Bork[5,17] & Jun Wang[1,4,6,11,18]

9,879,896 genes
(n=1,267 adult participants)

Nature Biotechnology 32, 834-841 (2014)

The Gut Microbiome Influences Remote Organ and Immune Responses



Neurological

Hsiao, E et al.
Cell 2015
Dae-Wook Kang et al
Microbiome. 2017

Cardiovascular

Koeth et al Nat.
Med. 19(5):576. 2013
Tang et al NEJM
2013
Wang et al Nature
2011

Respiratory

Arietta, C.E. et al, Sci.
Transl. Med 2015
Fujimura, K.E., et al,
Nature Medicine 2016

Immunity

Trompette et al
Nature Medicine,
2014
Fonseca et al,
Mucosal
Immunity 2017

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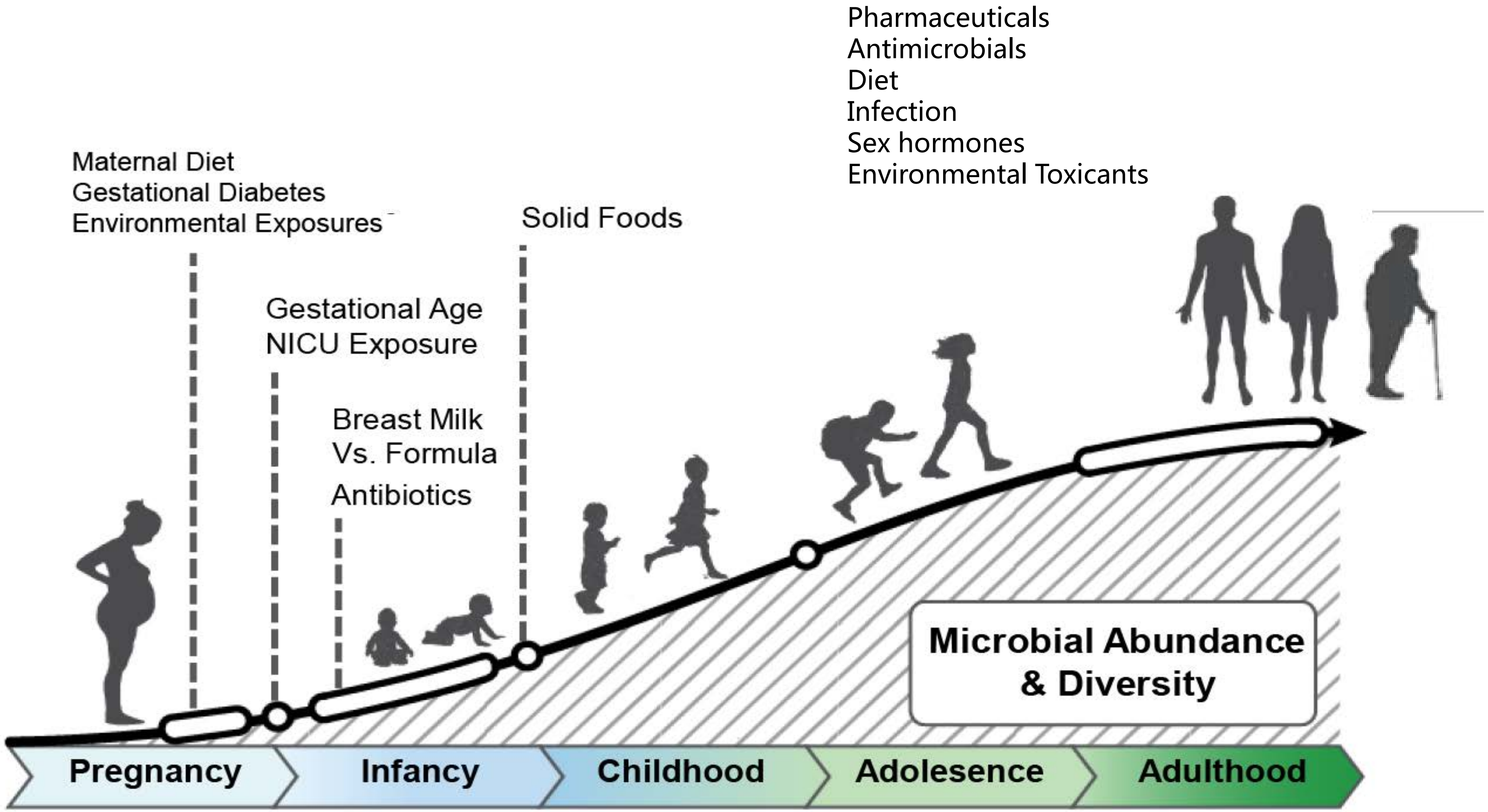
The Gut Microbiome Evolves Over Human Lifespan



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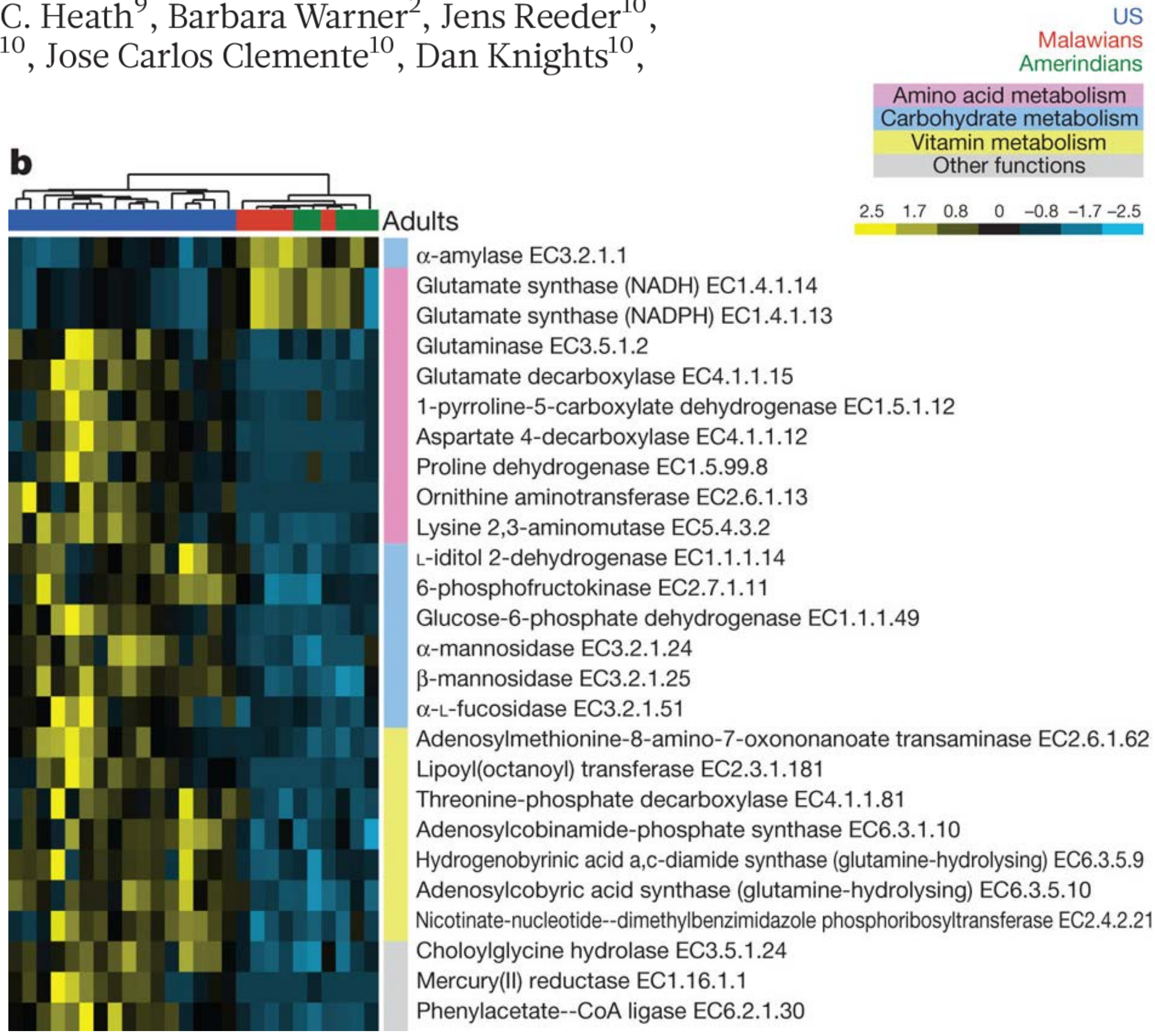
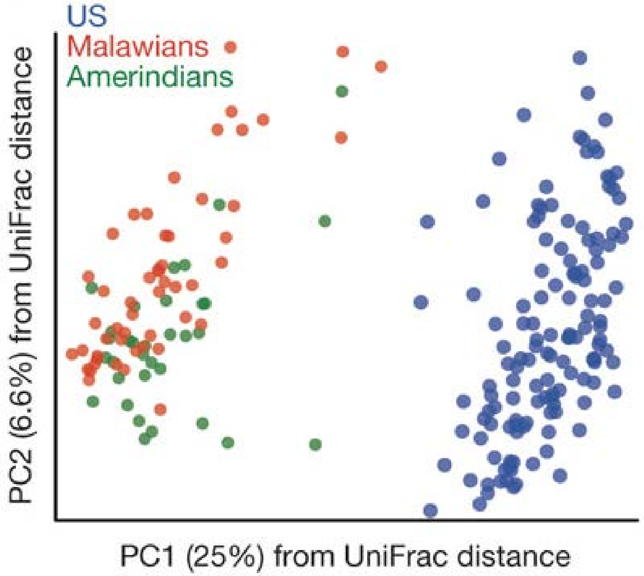
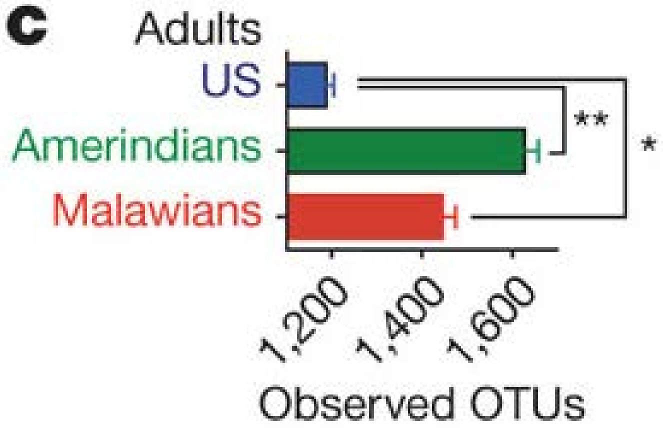
Environmental Chemicals, the Human Microbiome, and Health Risk: A Research Strategy. National Academy of Science and Engineering Report

Human gut microbiome viewed across age and geography

Tanya Yatsunenko[1], Federico E. Rey[1], Mark J. Manary[2,3], Indi Trehan[2,4], Maria Gloria Dominguez-Bello[5], Monica Contreras[6], Magda Magris[7], Glida Hidalgo[7], Robert N. Baldassano[8], Andrey P. Anokhin[9], Andrew C. Heath[9], Barbara Warner[2], Jens Reeder[10], Justin Kuczynski[10], J. Gregory Caporaso[11], Catherine A. Lozupone[10], Christian Lauber[10], Jose Carlos Clemente[10], Dan Knights[10], Rob Knight[10,12] & Jeffrey I. Gordon[1]







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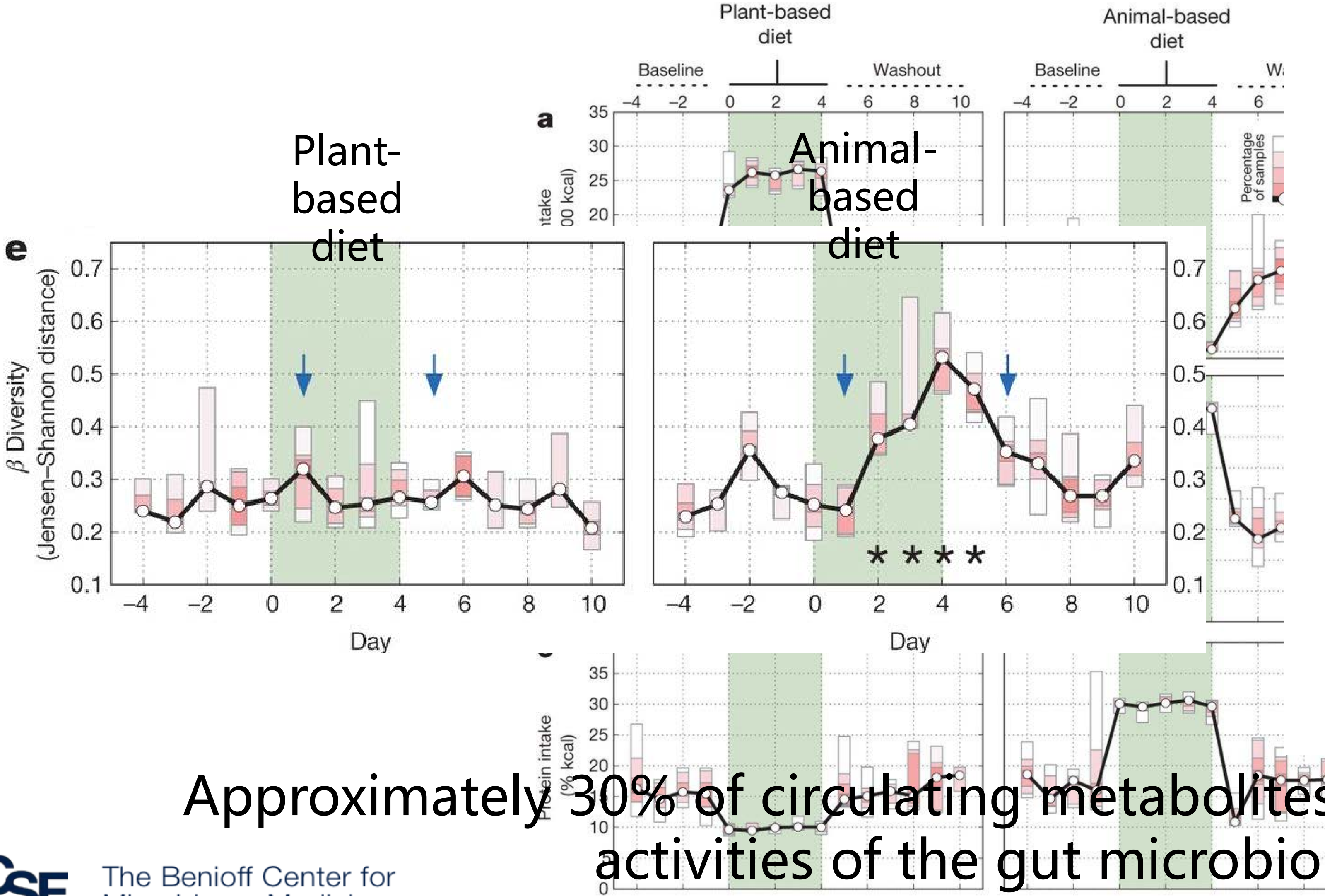
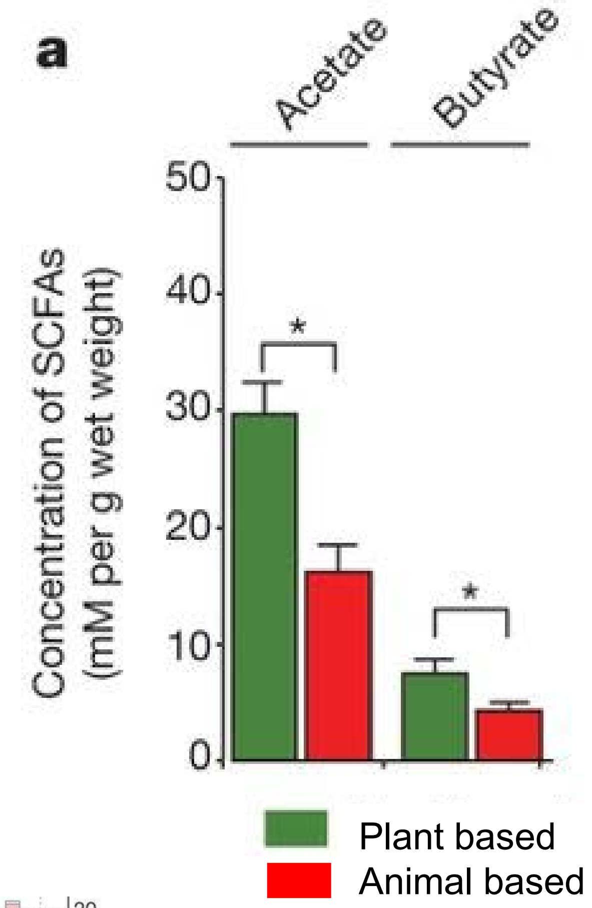
Diet Rapidly and Reproducibly Alters the Gut Microbiome





Approximately 30% of circulating metabolites are attributable to activities of the gut microbiome

David, L.A. et al. *Nature* **volume 505**, pages 559–56

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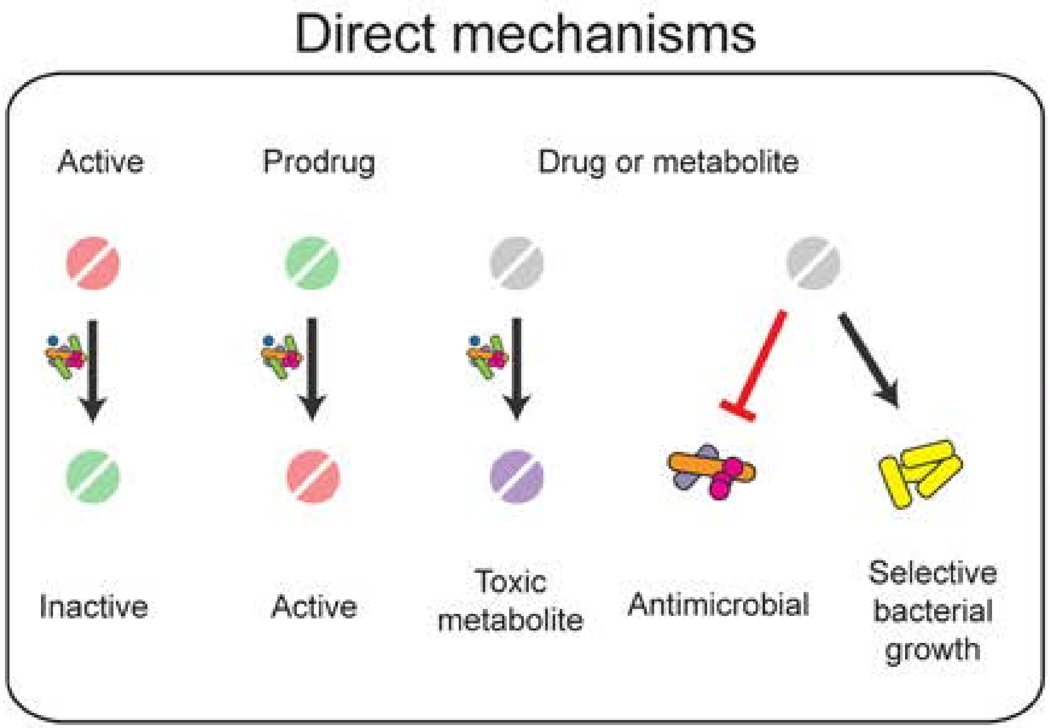
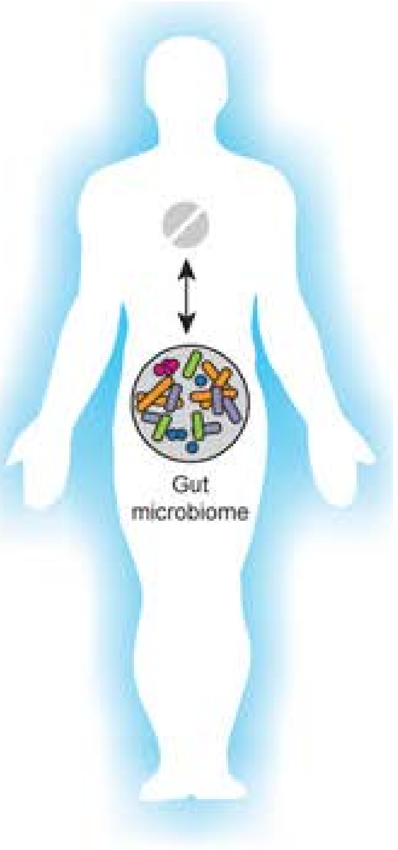
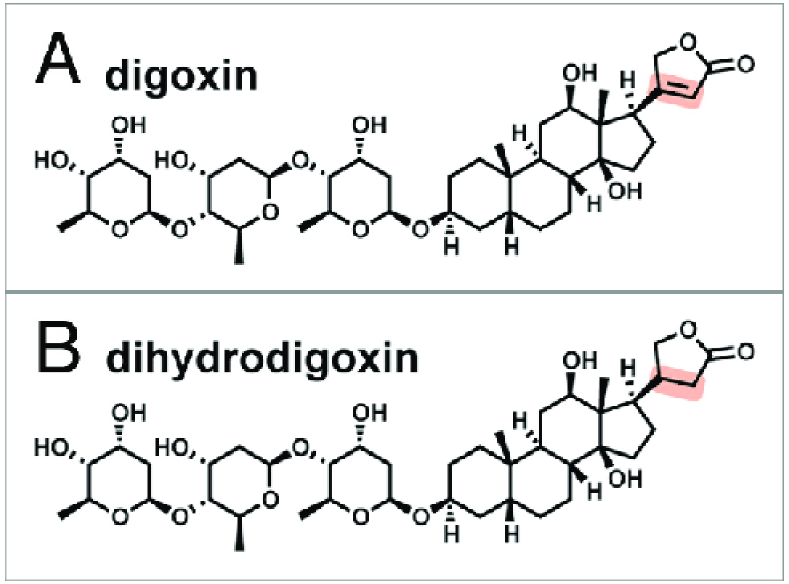
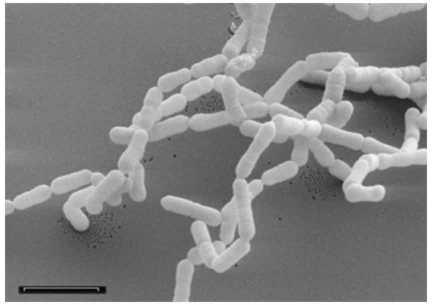
The Gut Microbiome Influences Drug Metabolism





Spanogiannopoulos, P et al Nat Rev Microbiol. 2016 14(5): 273–287.

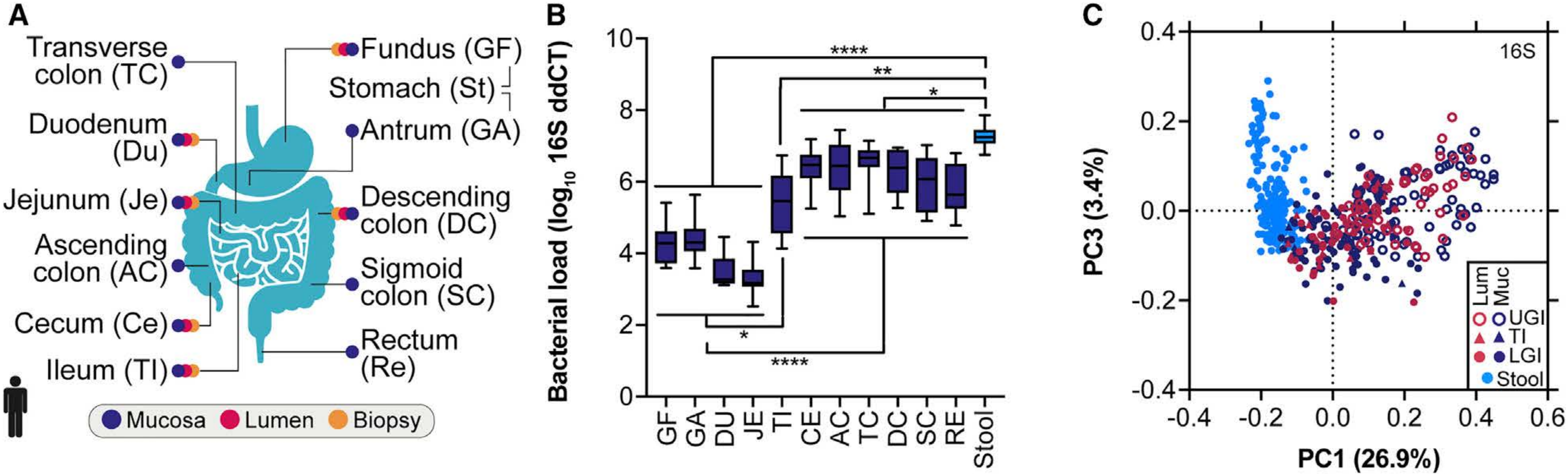




Eggertella lenta

Hasier, H. et al Science. 2013 Jul 19; 341(6143): 295–298.

Niche-specific Microbiomes Exist Along the Length of the Gastrointestinal Tract

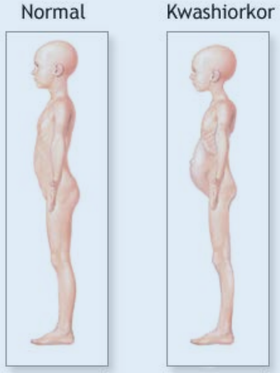


Zmora et al., 2018, Cell *174*, 1388–1405
September 6, 2018 © 2018 Elsevier Inc.
https://doi.org/10.1016/j.cell.2018.08.041

Human Microbiome – a Lever on Host Physiology.

OBESITY

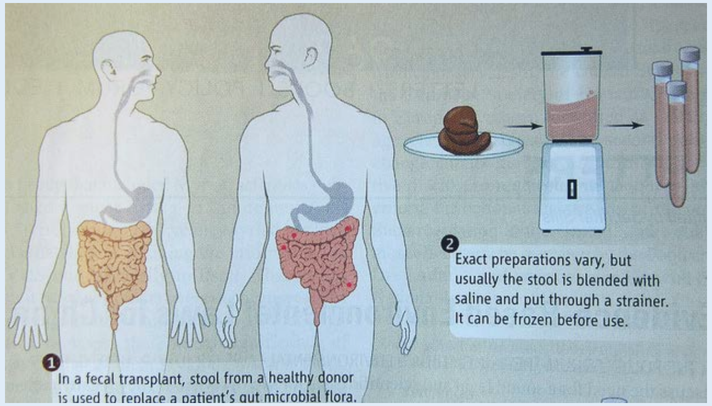
KWASHIKOR



AUTISM SPECTRUM
DISORDER

C. difficile
INFECTION

PEDIATRIC
AUTISM SPECTRUM
DISORDER



① In a fecal transplant, stool from a healthy donor is used to replace a patient's gut microbial flora.

② Exact preparations vary, but usually the stool is blended with saline and put through a strainer. It can be frozen before use.

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A Watershed Moment in Human Biology

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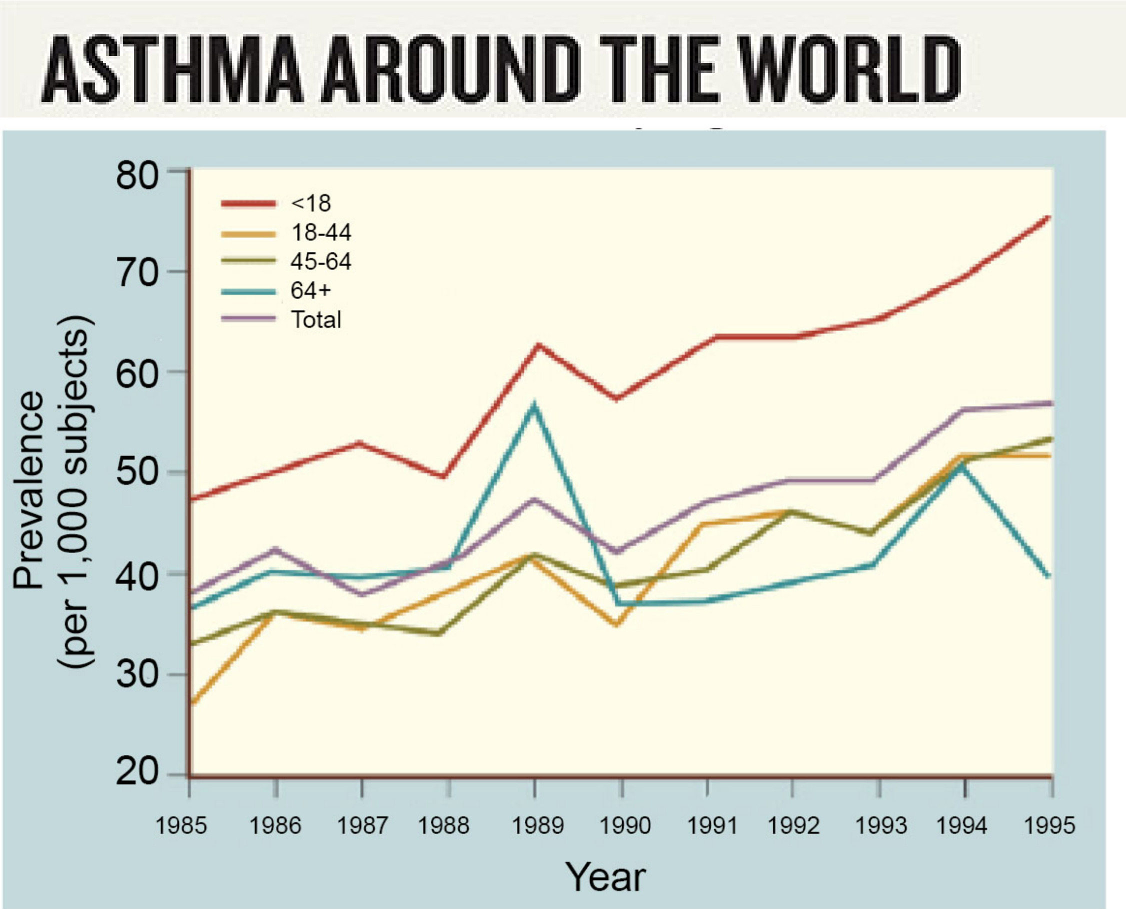
Asthma is Prevalent in Westernized Nations



Global Iniative for Asthma

Allergic Asthma

Reduced

IL10

Regulatory T cells

Increased

IL4
IL5
IL13

T2

IgE

Lloyd et al Immunity. 2009 438–449.

NO CURE > PREVENTION

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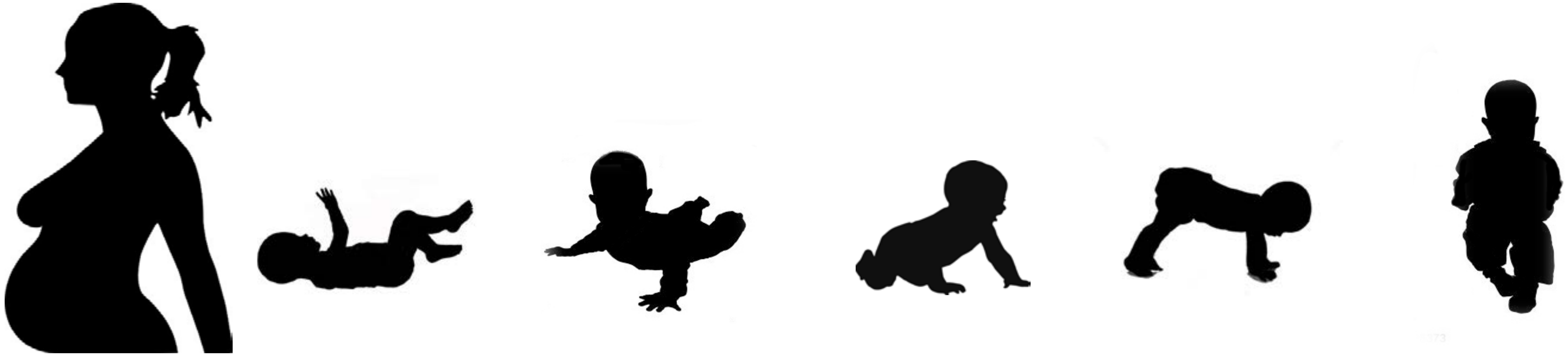
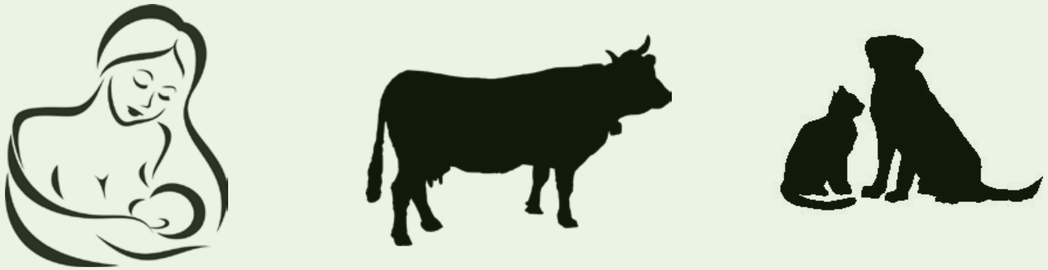
Graham-Rowe, D. Nature 479, S2–S4 (2011)

INCREASED RISK FOR ALLERY and ASTHMA

C-section





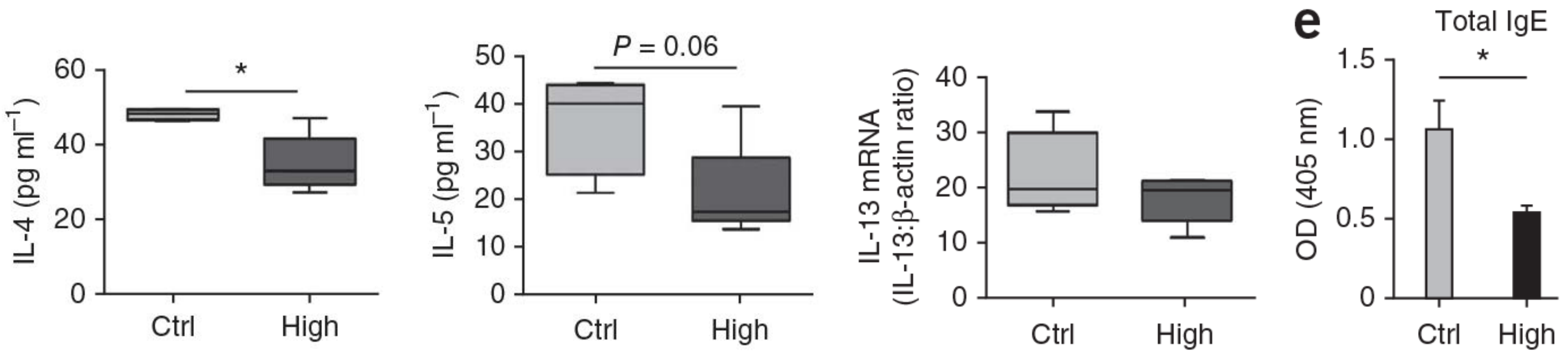
DECREASED RISK FOR ALLERY and ASTHMA

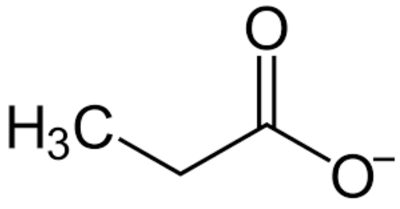
Gut Microbial-derived Metabolites Influence Airway Immunity

Poorly fermentable fiber
(Control diet)

Highly fermentable pectin
(High-fiber)

→ House Dust Mite Airway Sensitization → Airway Allergic Response

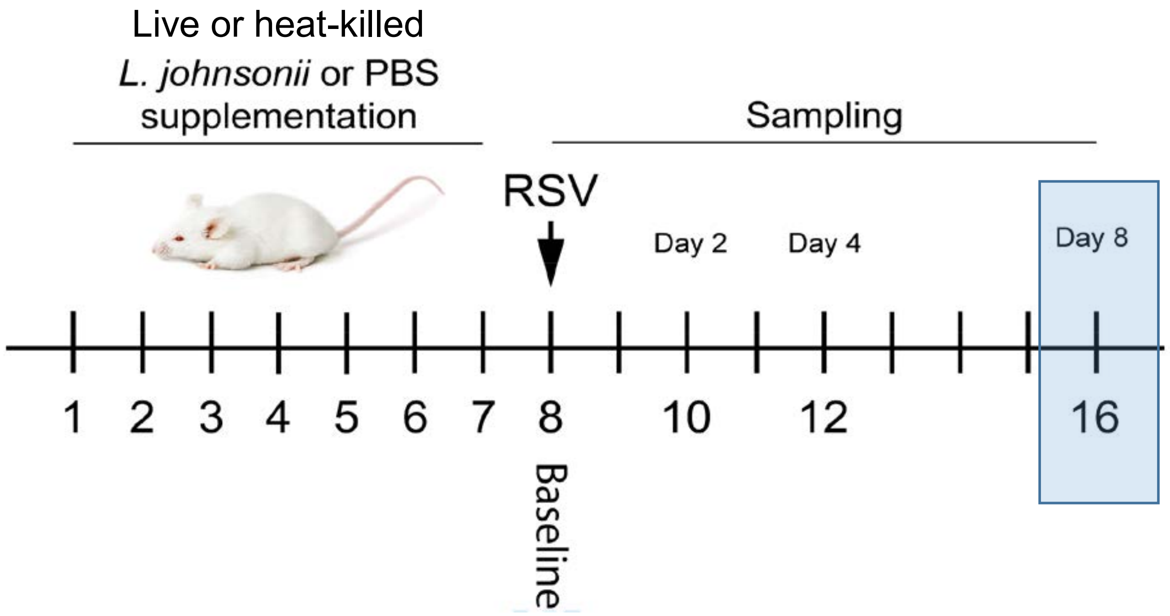


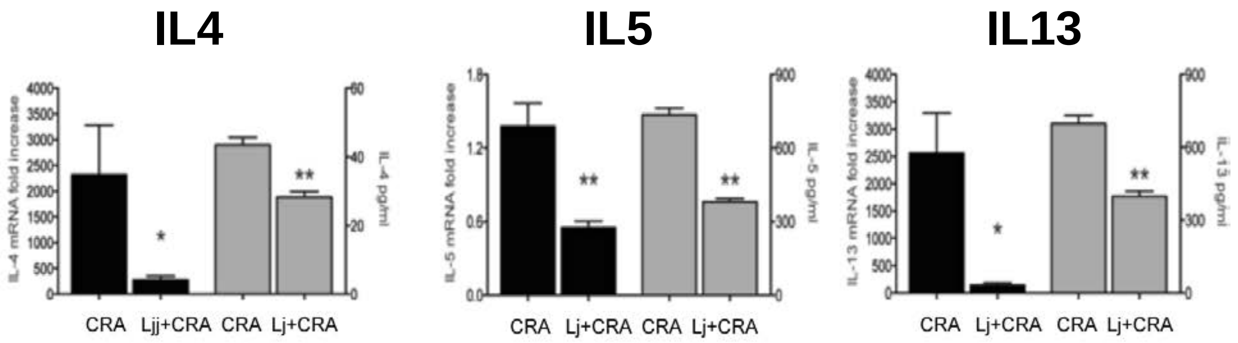


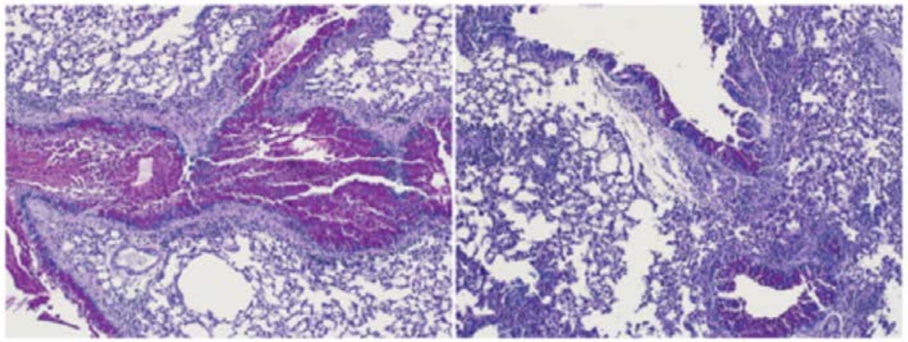
Propionate

Trompette et al Nature Medicine. 20, 159-166 (2014)

Gut Microbiome Manipulation Alters Airway Mucosal Response to Allergen Challenge or Viral Infection







CRA

CRA + *Lactobacillus* spp.

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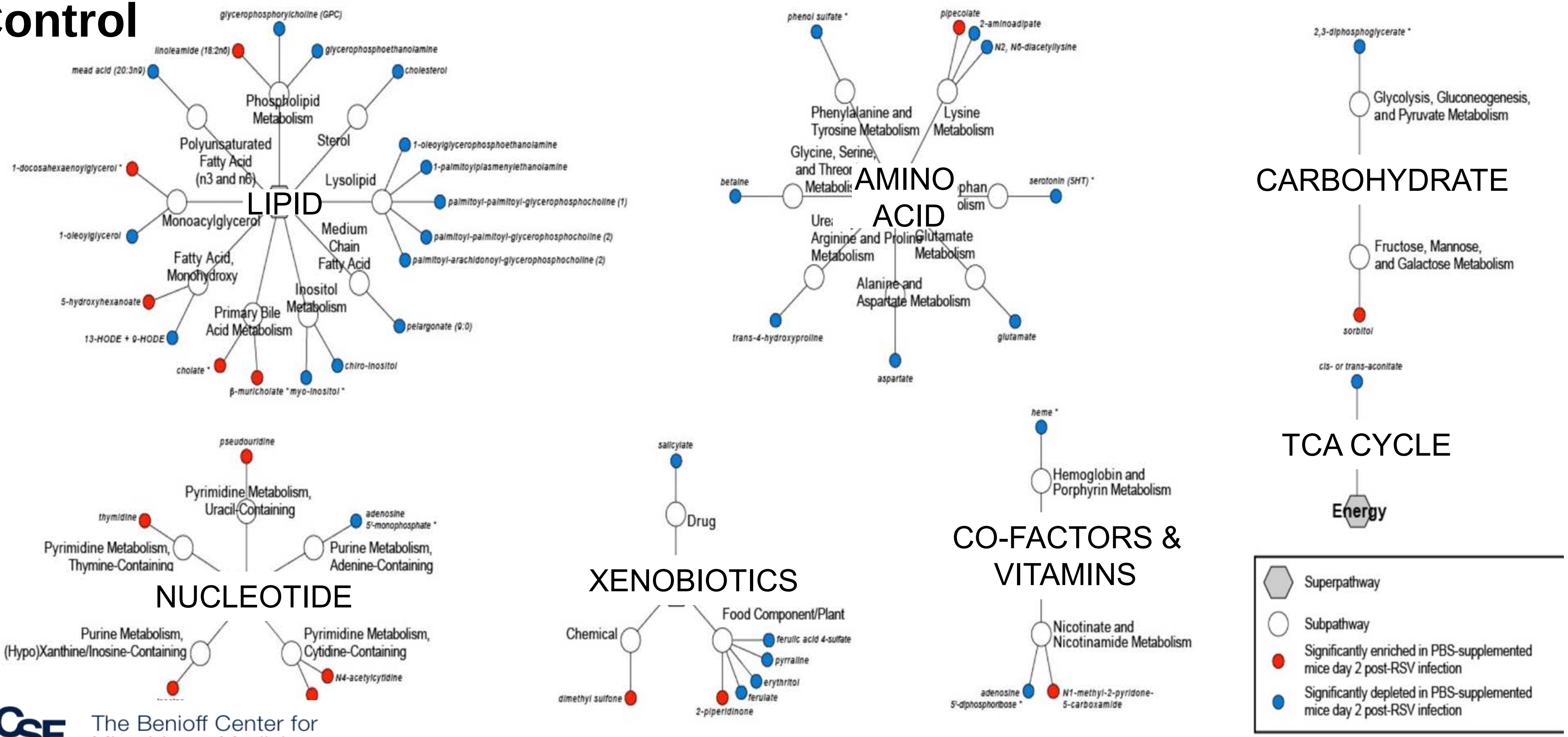
Fujimura at al. Proc Natl Acad Sci U S A. 2014 Jan 14;111(2):805-10.

Gut Microbiome Manipulation Alters Serum Metabolic Response to Viral Respiratory Infection

Control



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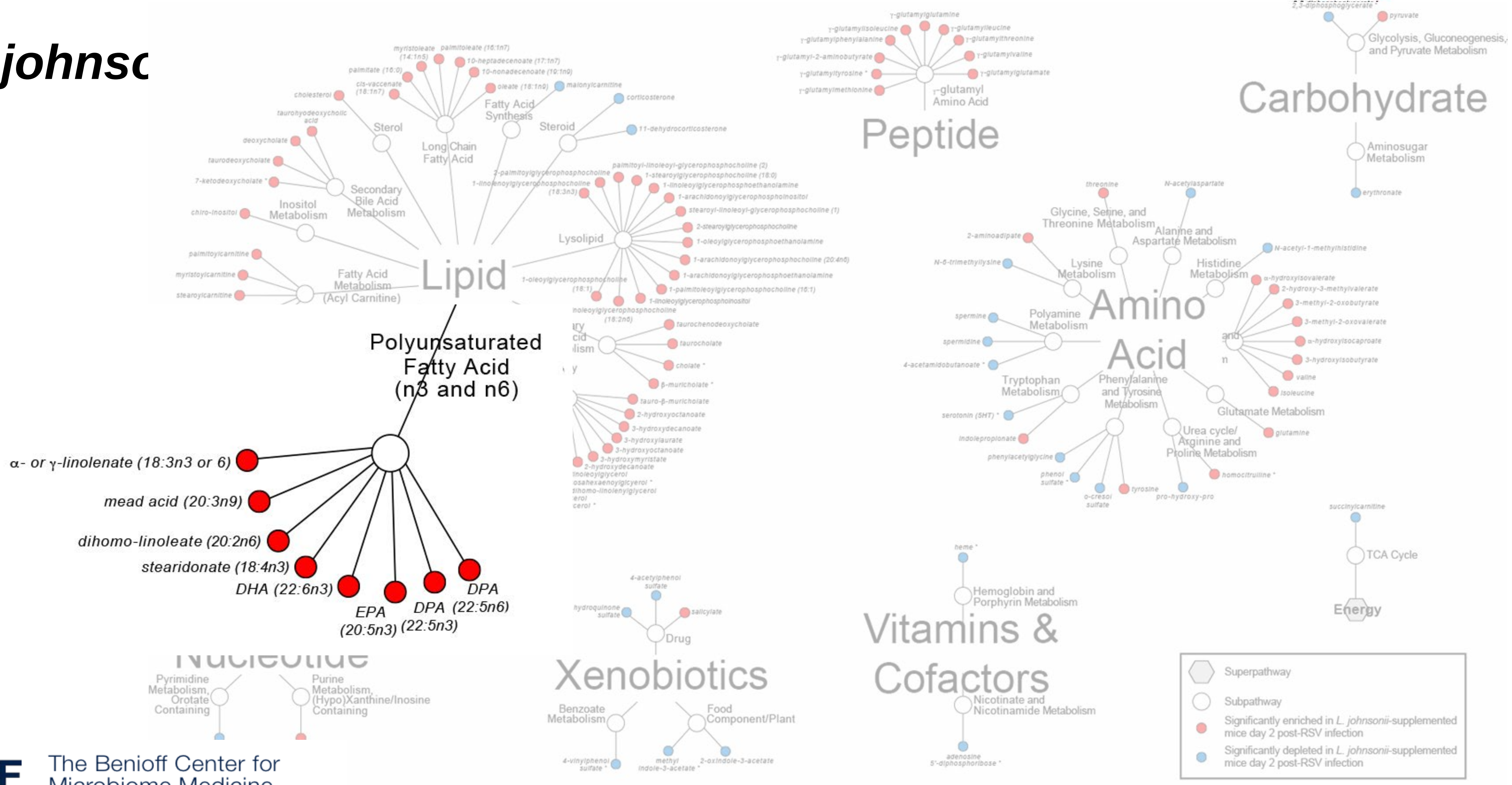
Fonseca et al. Mucosal Immunol. 2017 Mar 15.

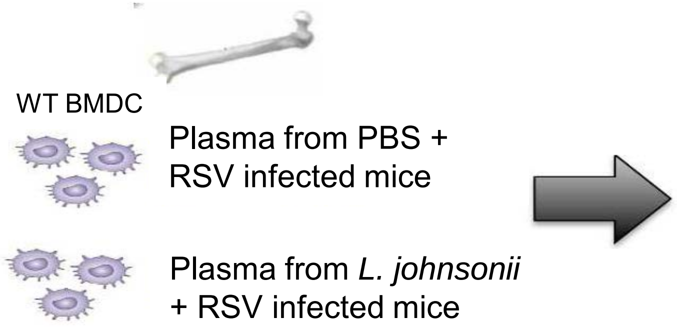
Gut Microbiome Manipulation Alters Peripheral Metabolic Response to Viral Respiratory Infection

L. johnso



Fonseca et al. Mucosal Immunol. 2017 Mar 15.

Gut Microbiome Influences Hematopoietic Cell Programing via Plasma-associated Mediators

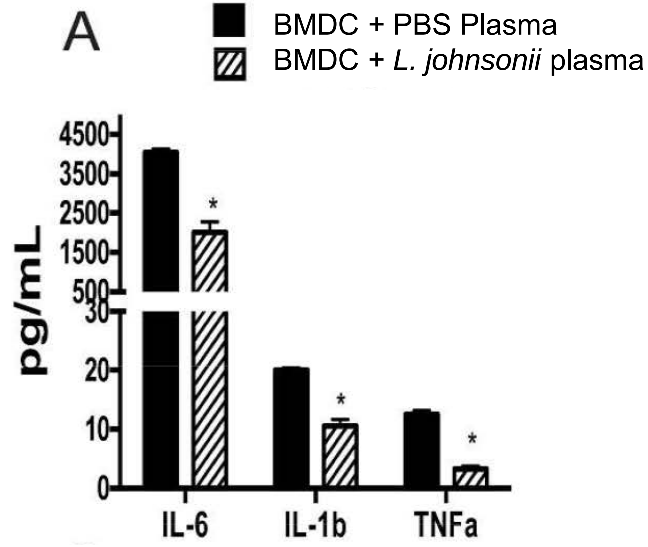


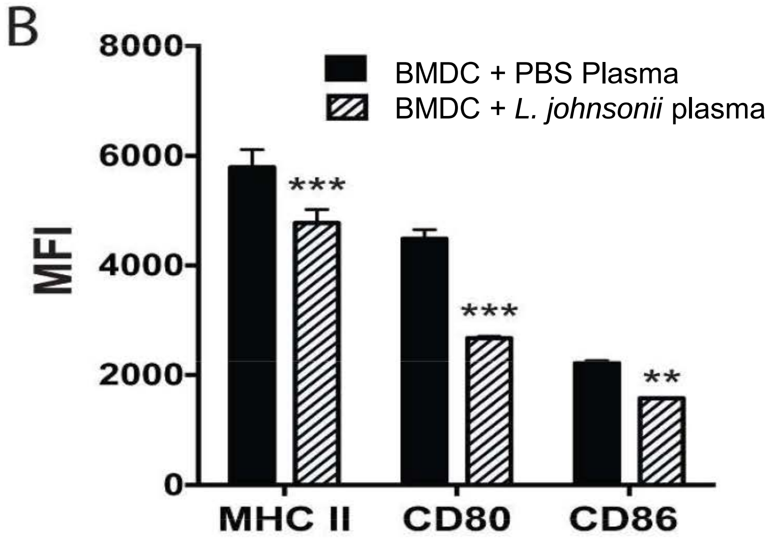
WT BMDC

Plasma from PBS + RSV infected mice

Plasma from *L. johnsonii* + RSV infected mice

BMDC infected with RSV for 24 h





BMDC: Bone marrow derived dendritic cells

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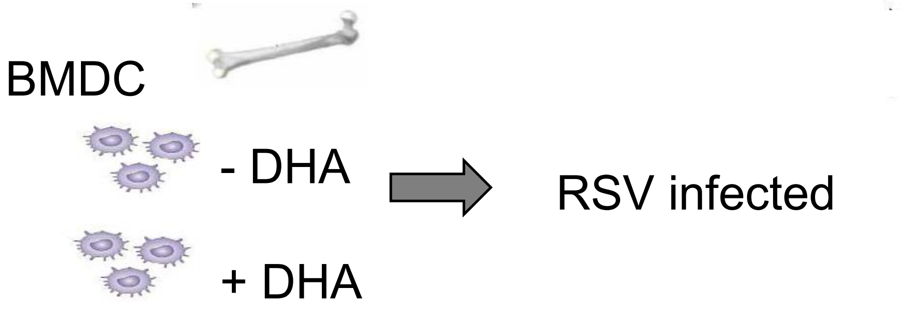
Fonseca et al. Mucosal Immunol. 2017 Mar 15.

Docosahexanoic Acid (DHA) inhibits RSV activation of BMDCs

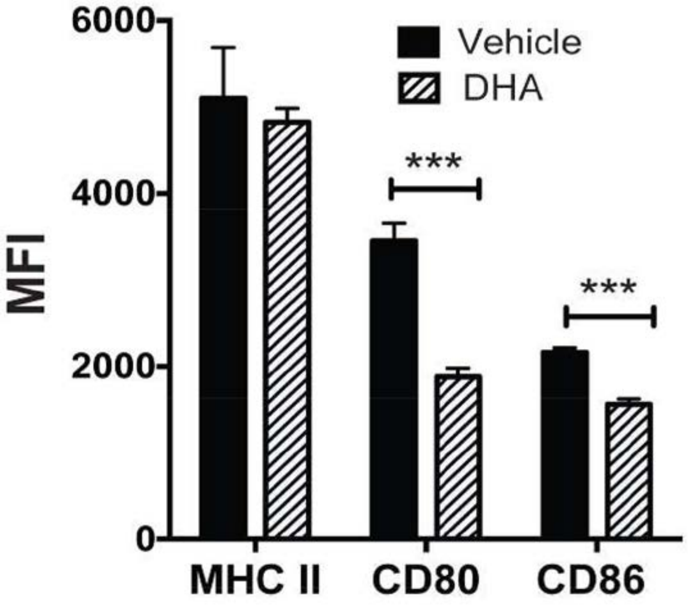


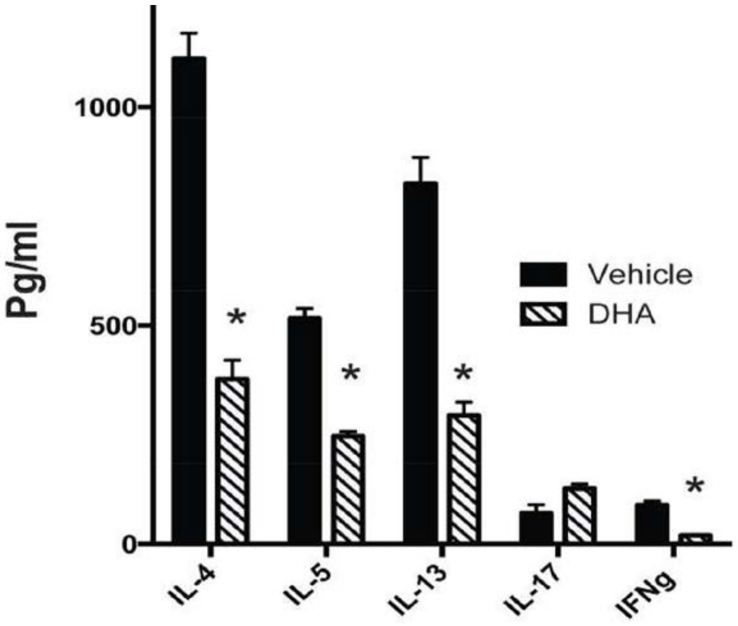
BMDC

- DHA

+ DHA

RSV infected

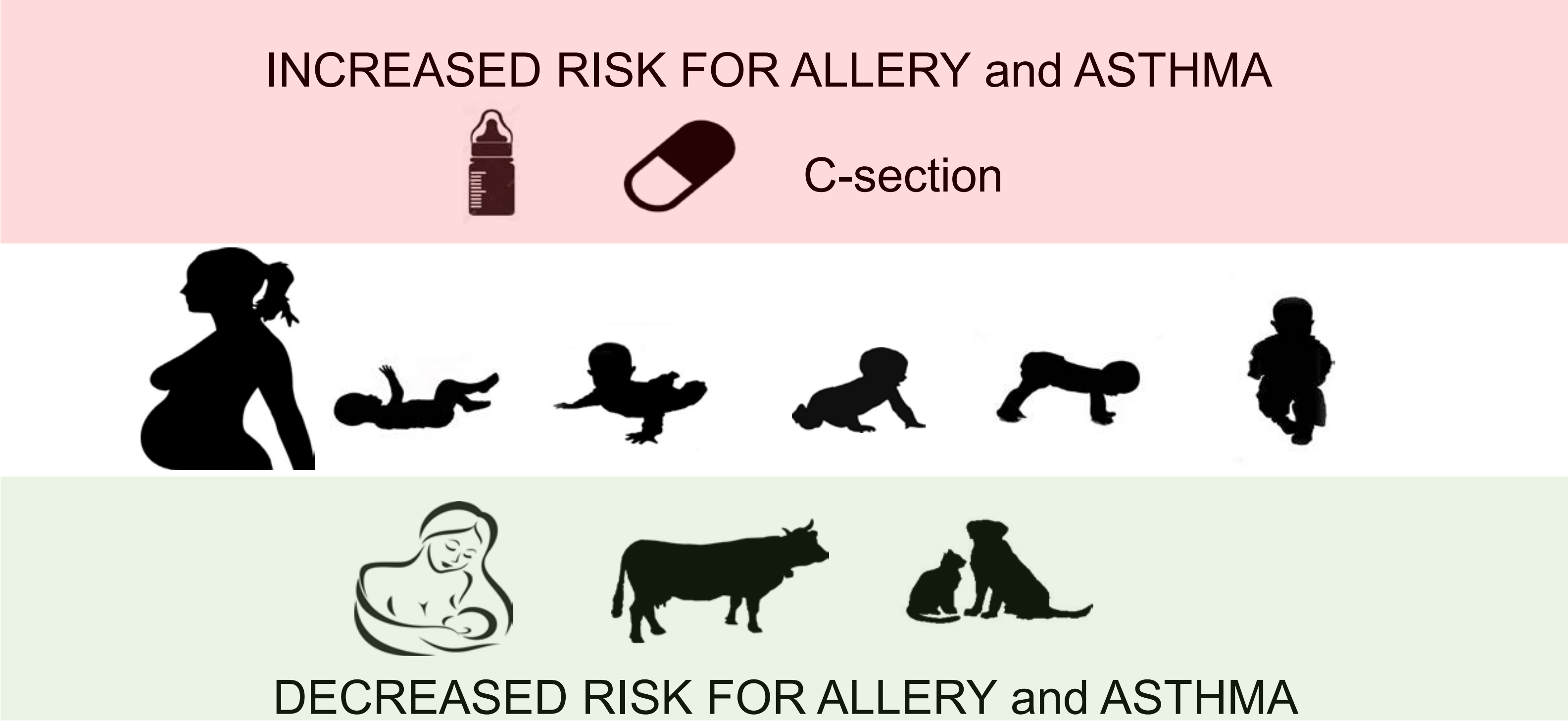




Circulating Products of the *L. johnsonii*-supplemented Gut Microbiome Down-regulate Pro-inflammatory Responses

Fonseca et al. Mucosal Immunol. 2017 Mar 15.

Could Early-life Gut Microbiome Perturbation and Metabolic Dysfunction Relate to Childhood Atopy and Asthma?

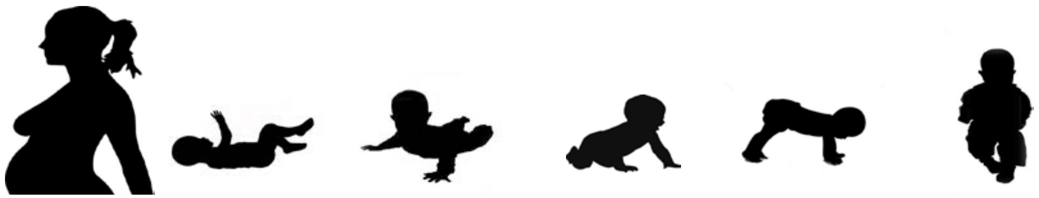


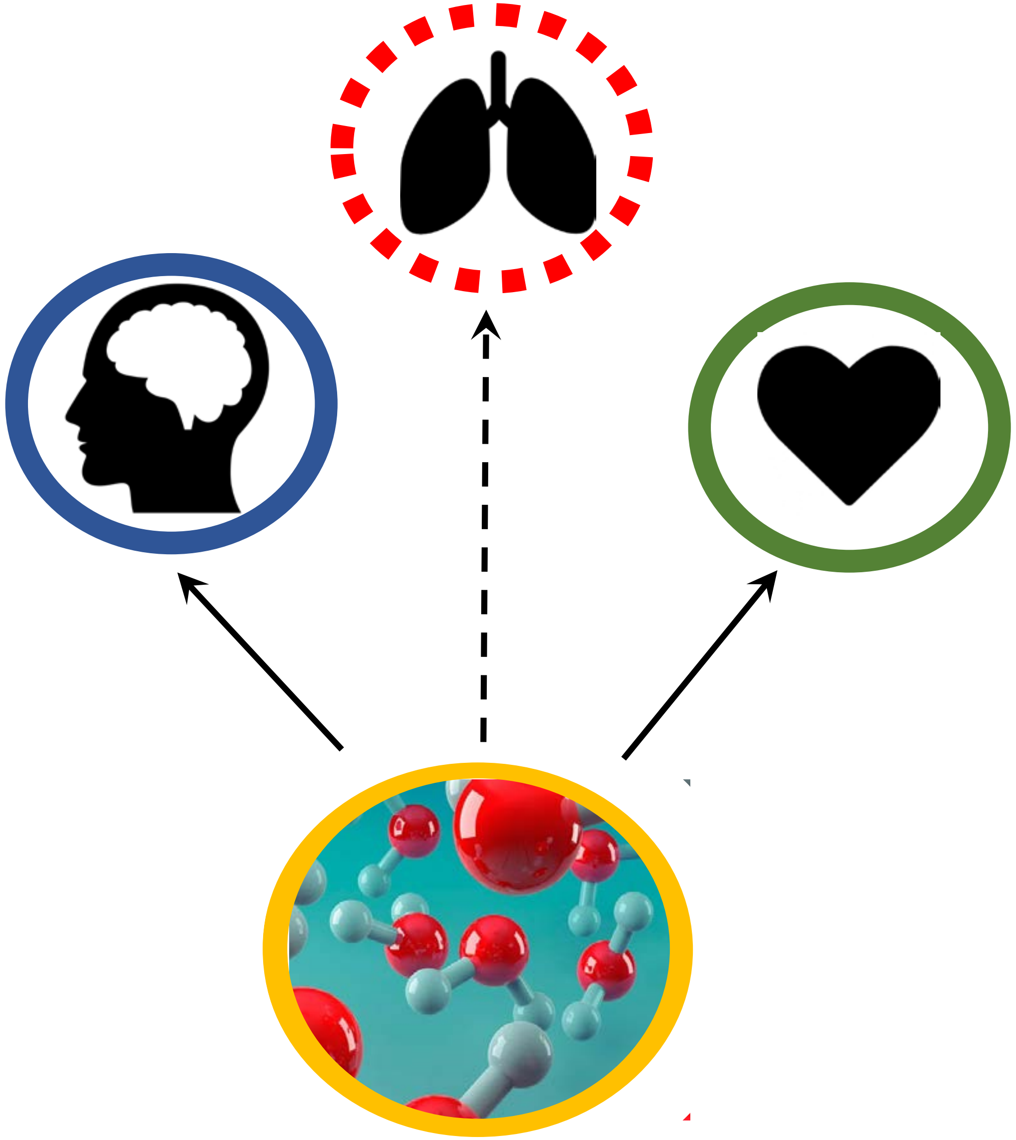
INCREASED RISK FOR ALLERY and ASTHMA

C-section

DECREASED RISK FOR ALLERY and ASTHMA

How Could the Neonatal Gut Microbiome Influence Airway Disease Development in Childhood?





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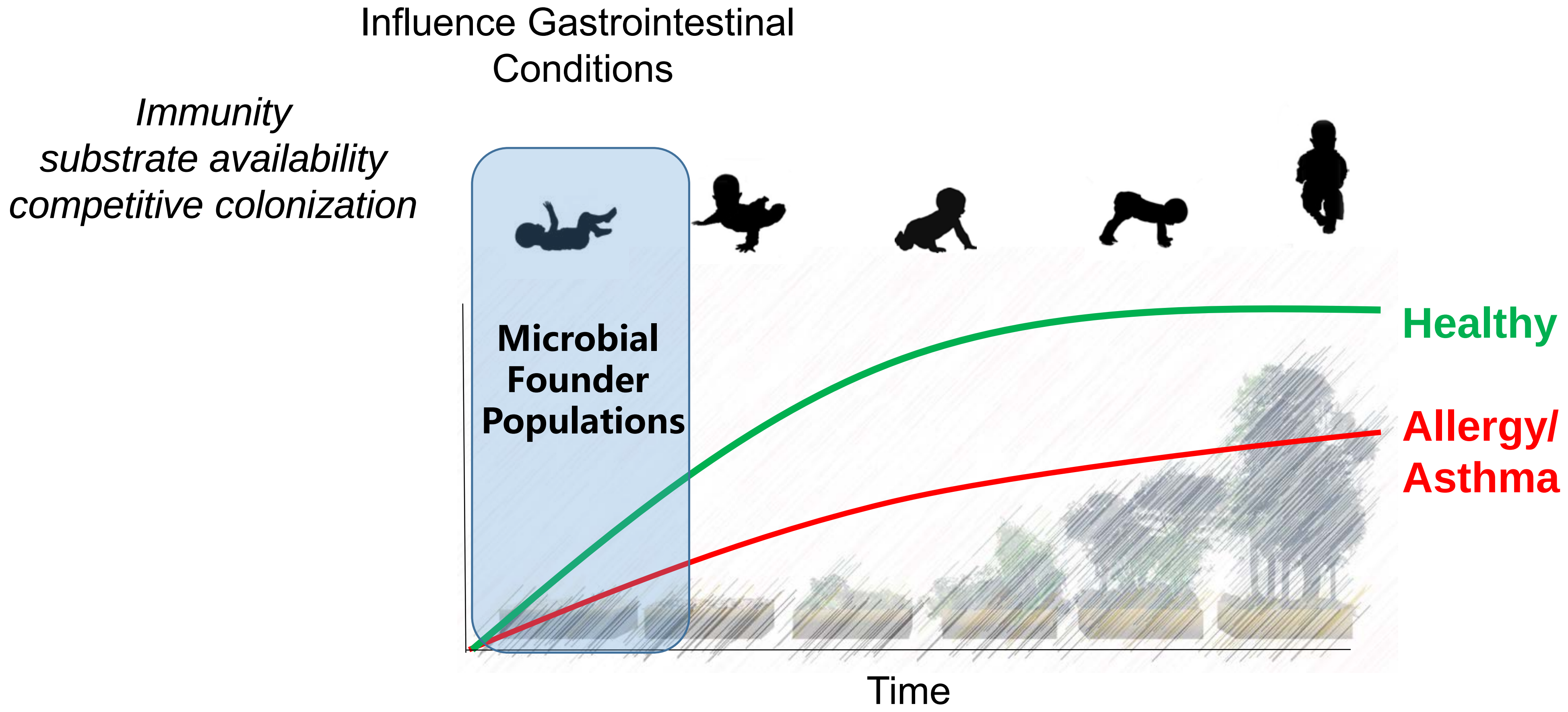
Hypothesis

Neonatal Gut Microbiome Predicts Childhood Allergy and Asthma and Offers Mechanistic Insights into the Origins of Disease



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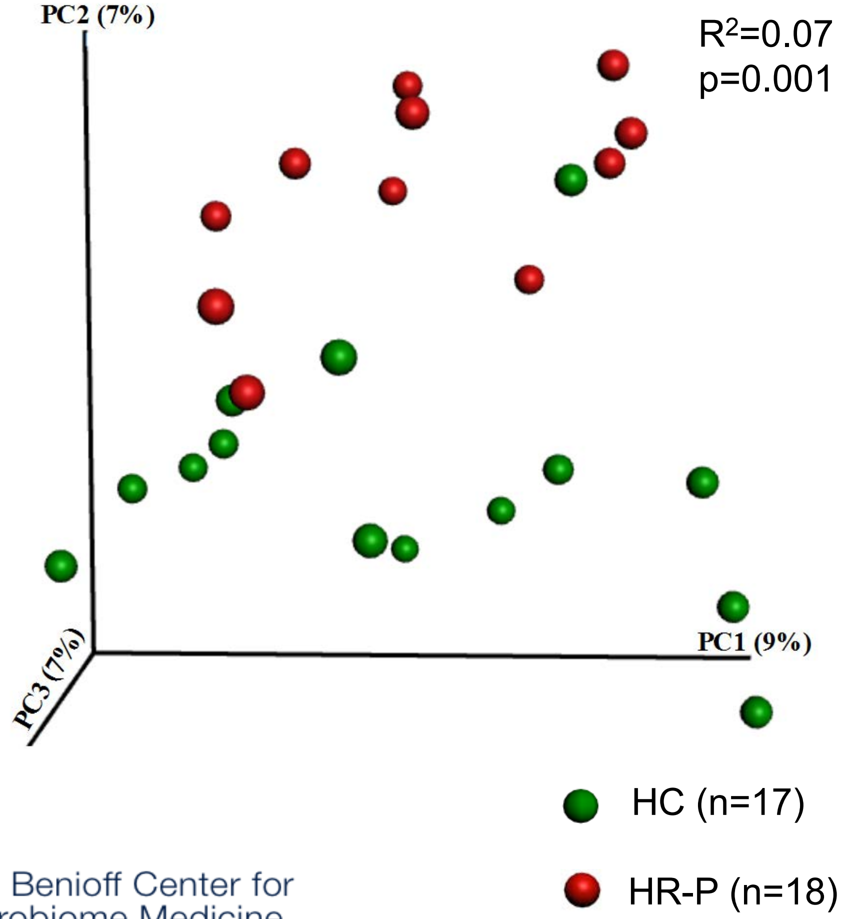
High-risk for Asthma Gut Microbiota is Distinct at Birth and Exhibits Delayed Development in Infancy


Meconium microbiota

$R^2=0.07$
$p=0.001$

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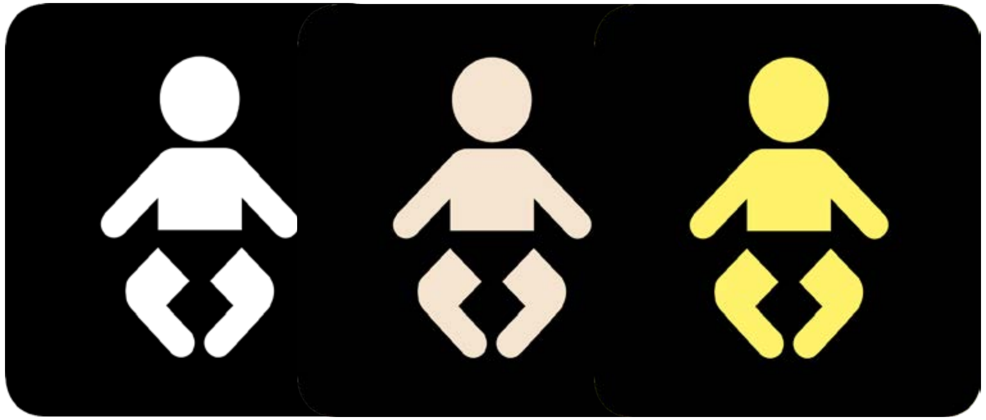
Durack, J. et al. Nature Communications. 2018

Wayne County Health, Environment, Allergy & Asthma Longitudinal Study (WHEALS)

Birth cohort



Neonates (1 month old)
N=130
Allergy at 2 years
Asthma at 4 years

16S rRNA (Bacteria) and ITS2 (Fungi) biomarker gene sequencing

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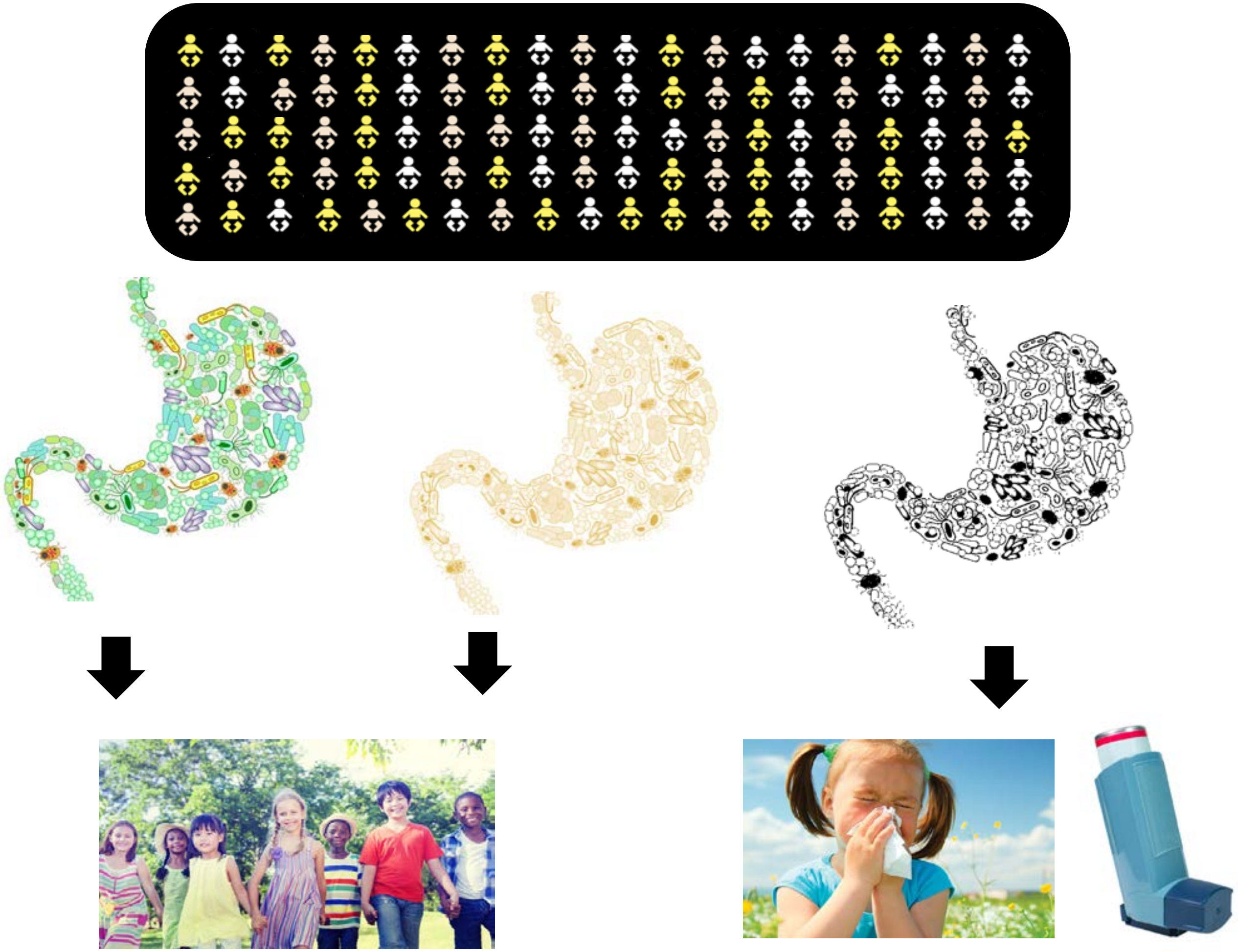
Distinct Neonatal Gut Microbiota Exist and Relate to Risk of Childhood Atopy and Asthma

1 month

2 years
4 years



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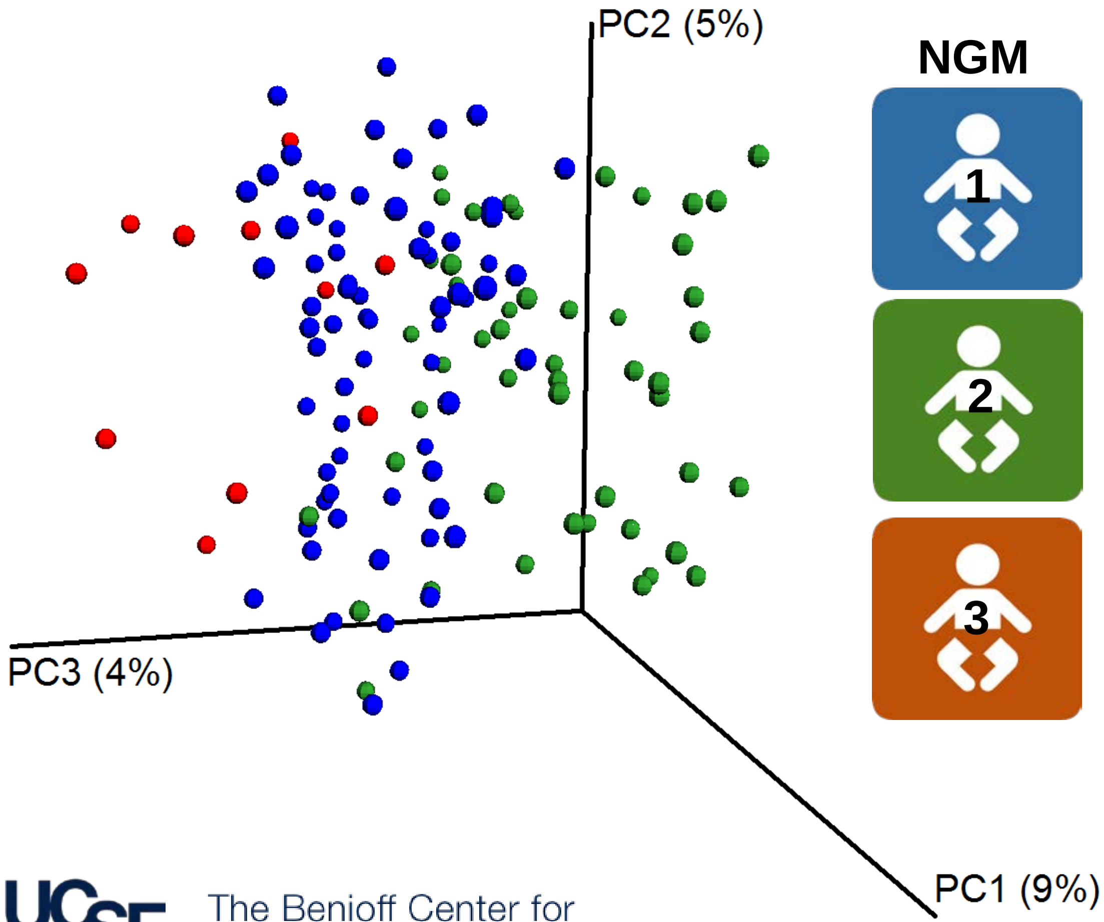
Fujimura, E. et al. Nature Medicine 2016

Neonatal Gut Microbiota State is Associated with Risk of Childhood Atopy and Asthma

$R^2=0.09, p<0.001$



	🟦 vs 🟩	🟧 vs 🟦	🟧 vs 🟩
Atopy (age 2 years)	1.43 (0.73-2.81) P=0.3	2.95 (1.42-6.09) P=0.004	2.06 (1.01-4.19) P=0.048
Asthma (age 4 years)	0.87 (0.31-2.50) P=0.87	2.95 (1.09-7.98) P=0.033	3.36 (1.10-10.3) P=0.034

NGM3

Inter-kingdom perturbation

- Depleted commensal bacteria
- Increased allergenic fungi

Metabolic dysfunction

- Reduced PUFA
- Increased 12,13 DiHOME

Fujimura, E. et al. Nat Med. 2016 Oct;22(10):1187-1191.

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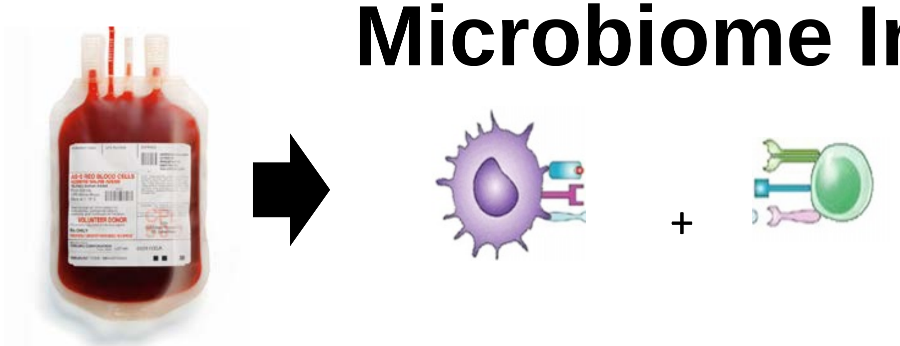
NGM1 NGM2

TOLEROGENIC GUT MICROBIOME

NGM3

PRO-ALLERGIC GUT MICROBIOME

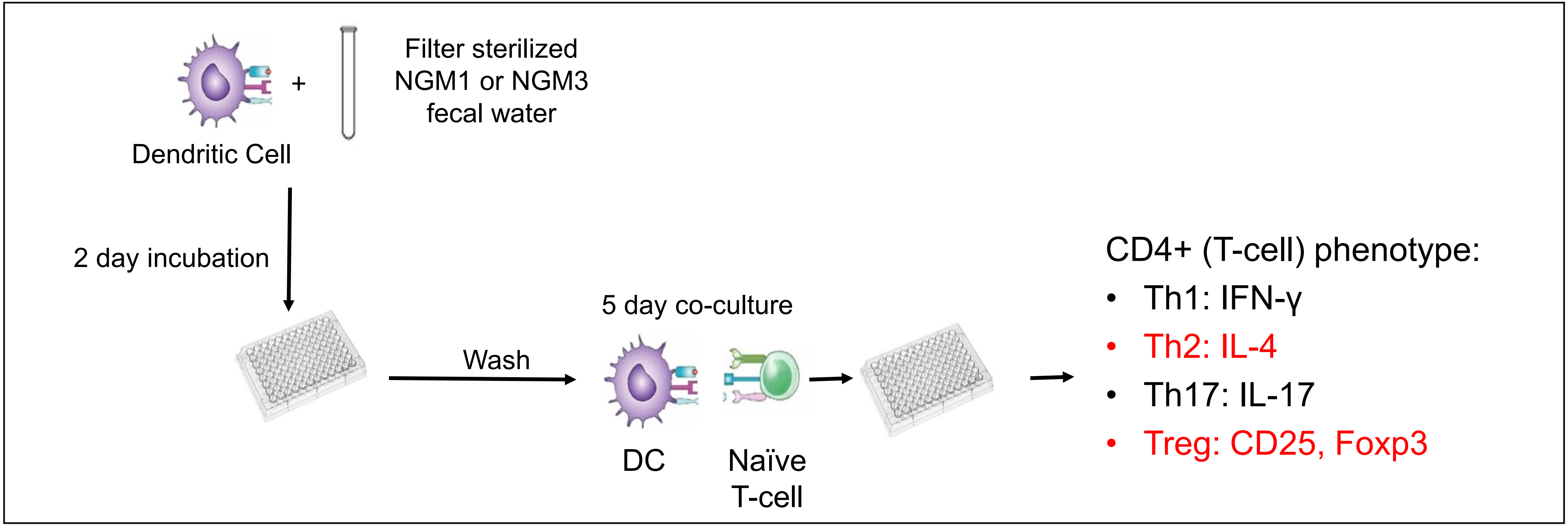
Human Immune Cell Assay to Assess Neonatal Gut Microbiome Immunostimulatory Capacity


Healthy Adult Donors

Dendritic Cells

+

Naïve T-cells


Dendritic Cell

+

Filter sterilized
NGM1 or NGM3
fecal water

2 day incubation

Wash

5 day co-culture

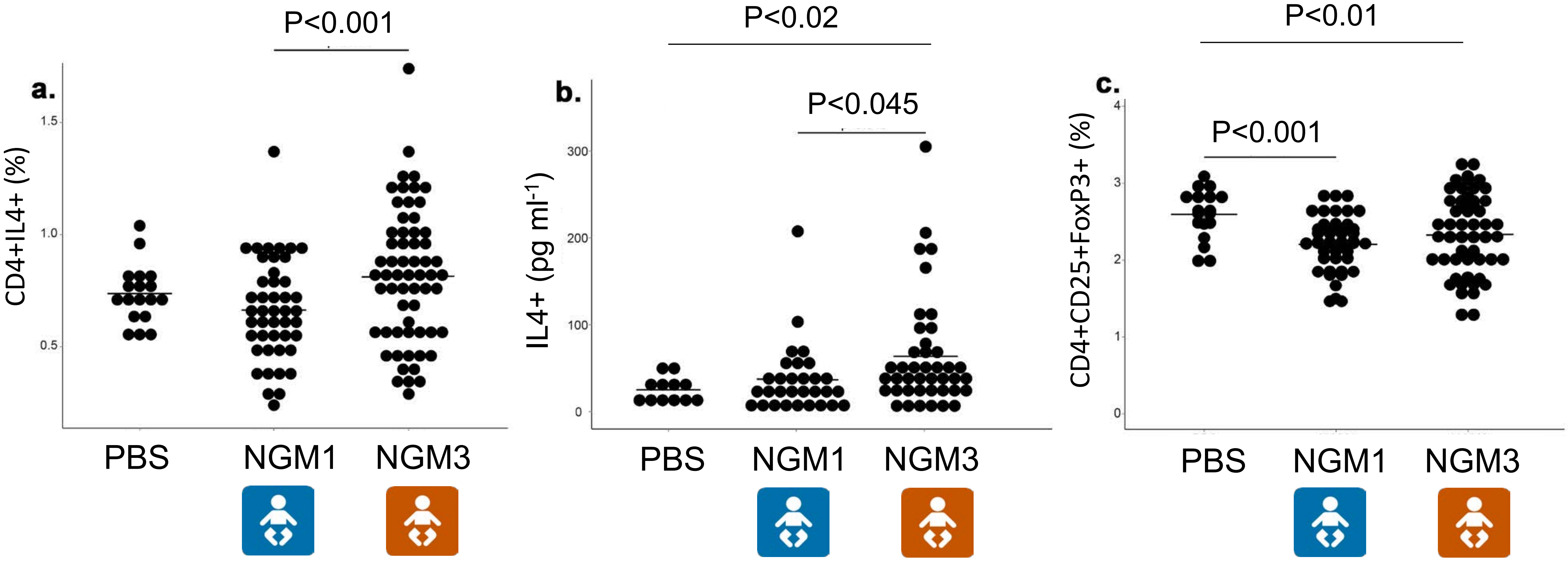
DC

Naïve
T-cell

CD4+ (T-cell) phenotype:
- Th1: IFN-γ
- Th2: IL-4
- Th17: IL-17
- Treg: CD25, Foxp3

Fujimura, E. et al. Nat Med. 2016 Oct;22(10):1187-1191.

High-risk Neonatal Gut Microbiome Induces Allergic Inflammation and Suppresses T-regulatory Cells



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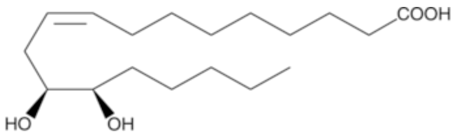
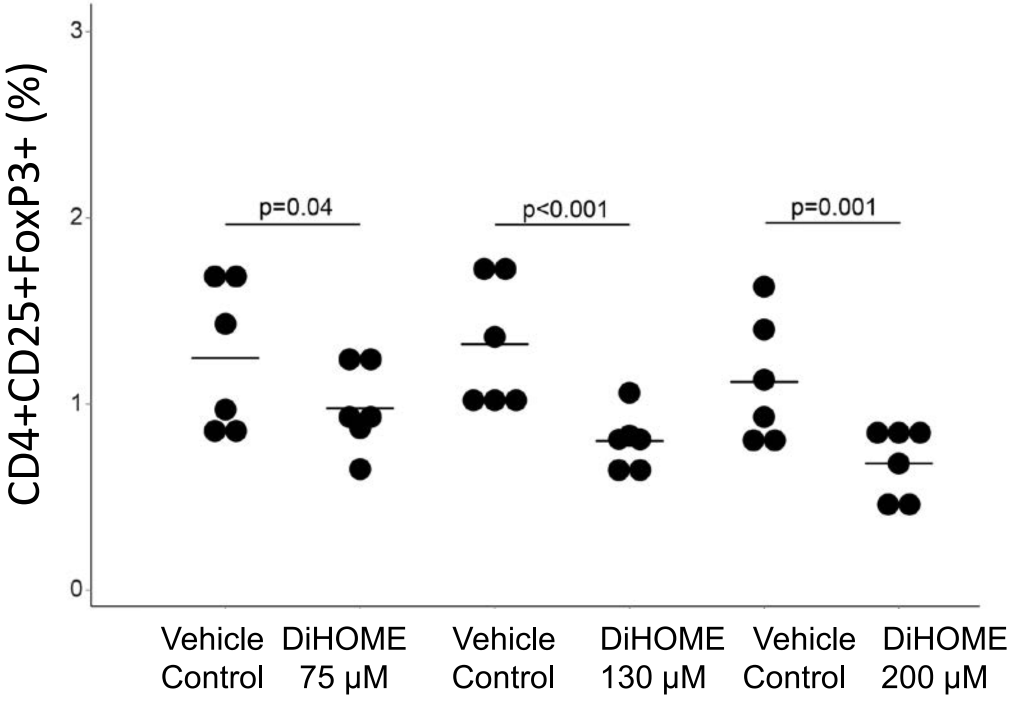
Fujimura, E. et al. Nat Med. 2016 Oct;22(10):1187-1191.

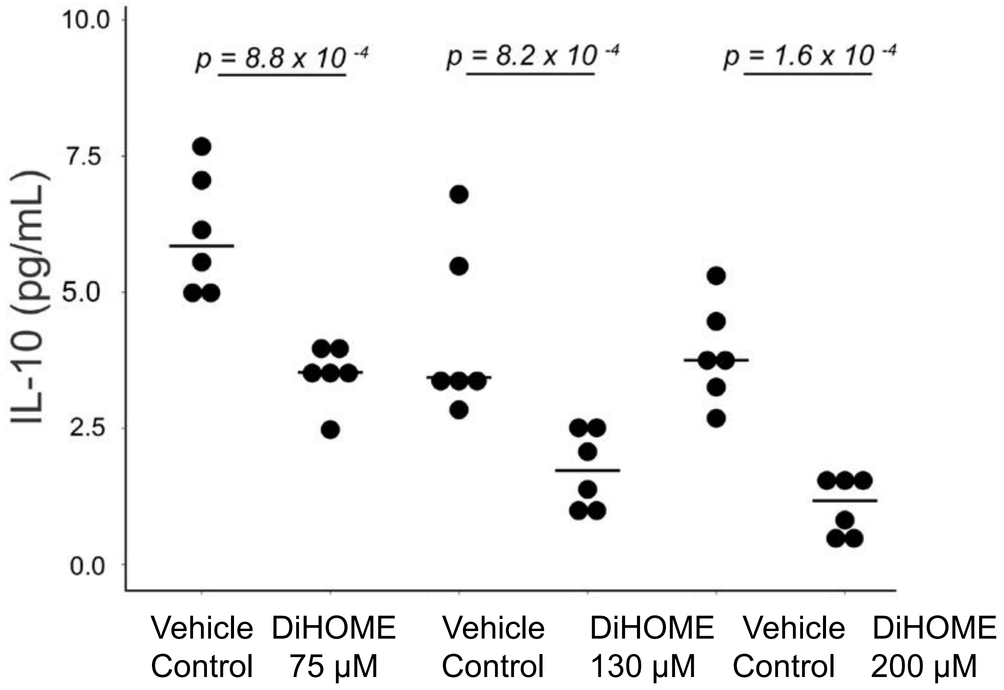
12,13 DiHOME Suppresses T-regulatory cell Populations *ex vivo*

3



12,13 DiHOME





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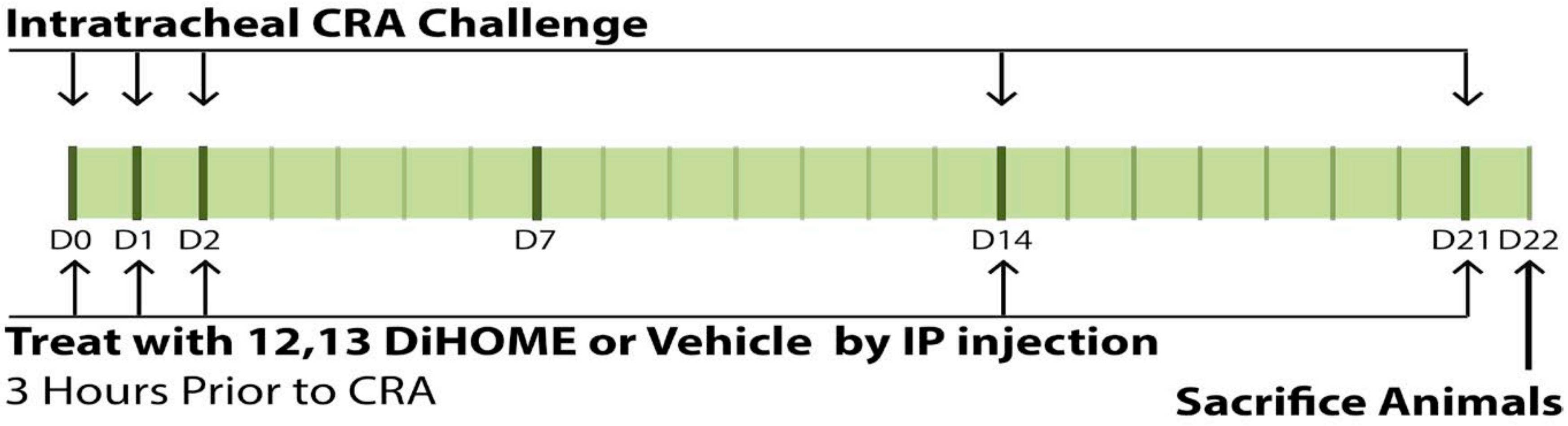
Fujimura, E. et al. Nat Med. 2016 Oct;22(10):1187-1191.

Can 12,13 DiHOME Promote Airway Allergic Sensitization in Mice?



Intratracheal CRA Challenge

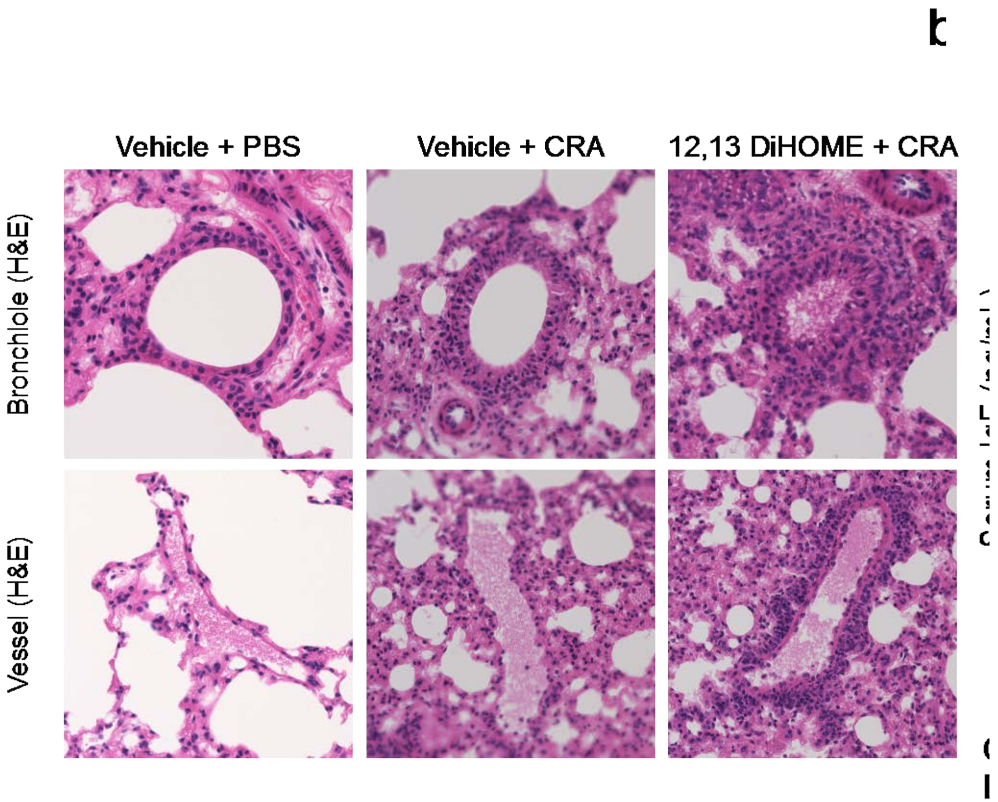
Treat with 12,13 DiHOME or Vehicle by IP injection

3 Hours Prior to CRA

Sacrifice Animals

Levan, S. *et al*, Nature Microbiology. 2019

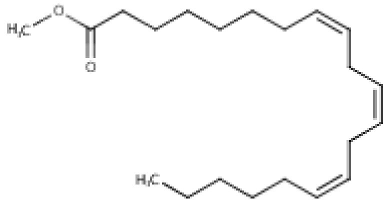
12,13 DiHOME Promotes Airway Allergic Sensitization and Increased Circulating IgE in Mice



Elevated concentrations of 12,13 DiHOME in the neonatal gut may promote allergic inflammation via reduction of T-reg frequency and activity

Levan, S. *et al*, Nature Microbiology. 2019

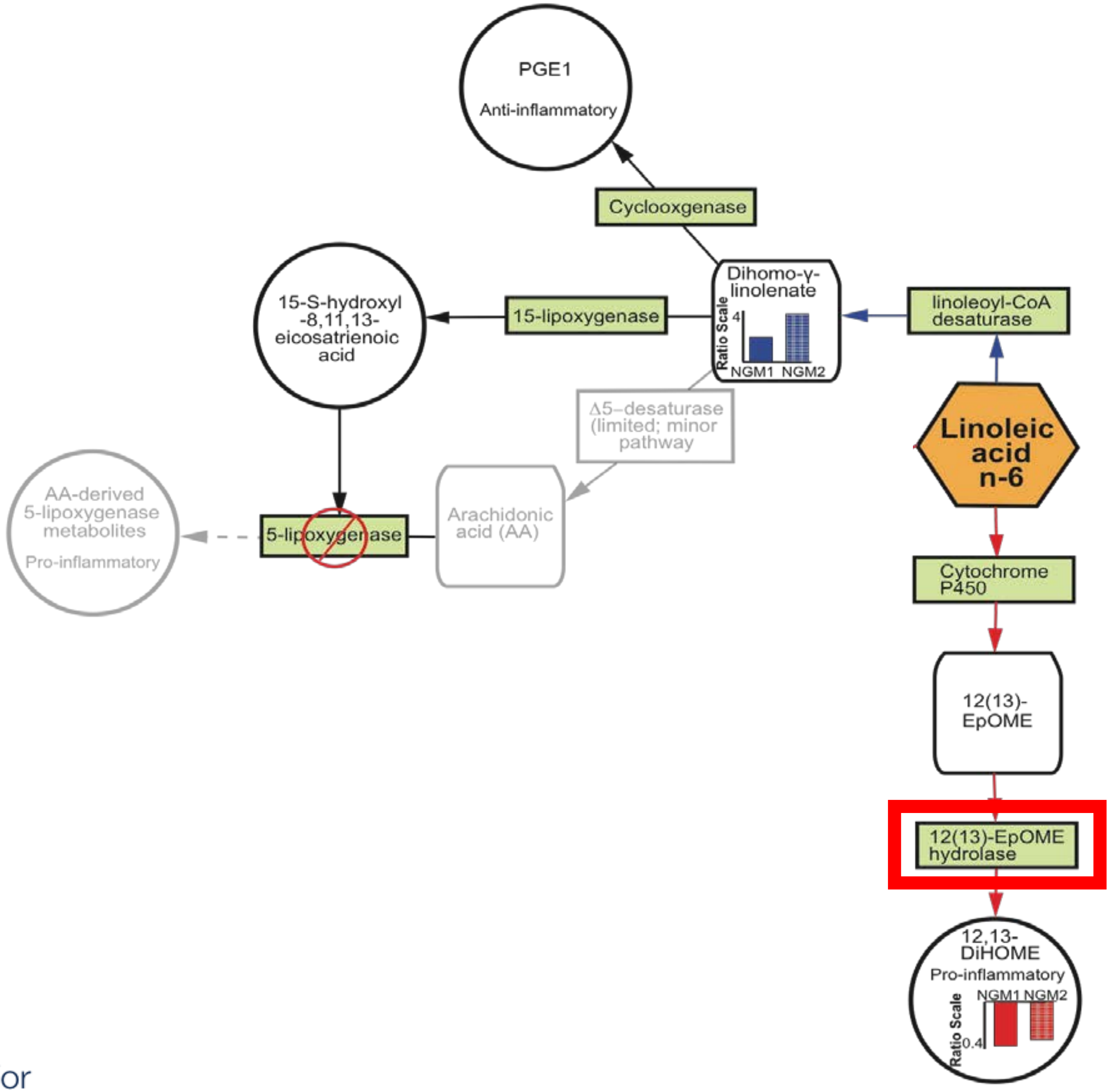
Altered Linoleic Acid Metabolism Characterizes High-risk Gut Microbiota



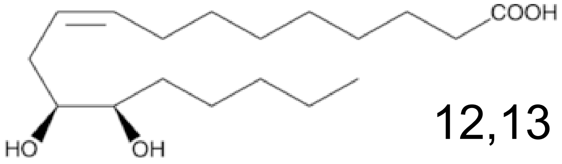
DiHomo-Ɣ-linoleate

2

1



3



12,13 DiHOME

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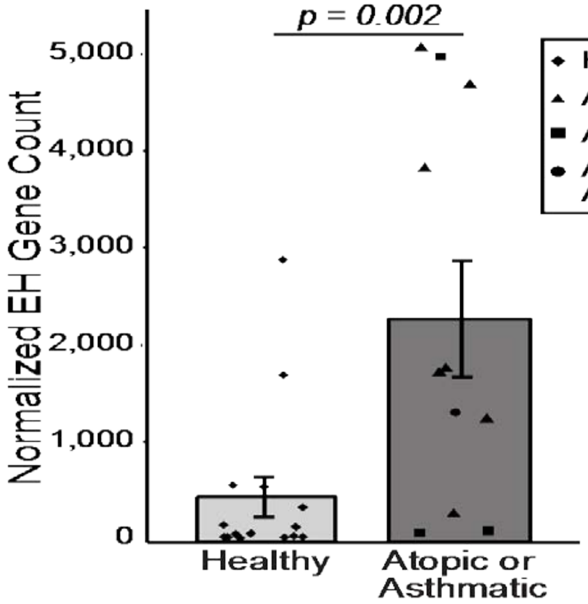
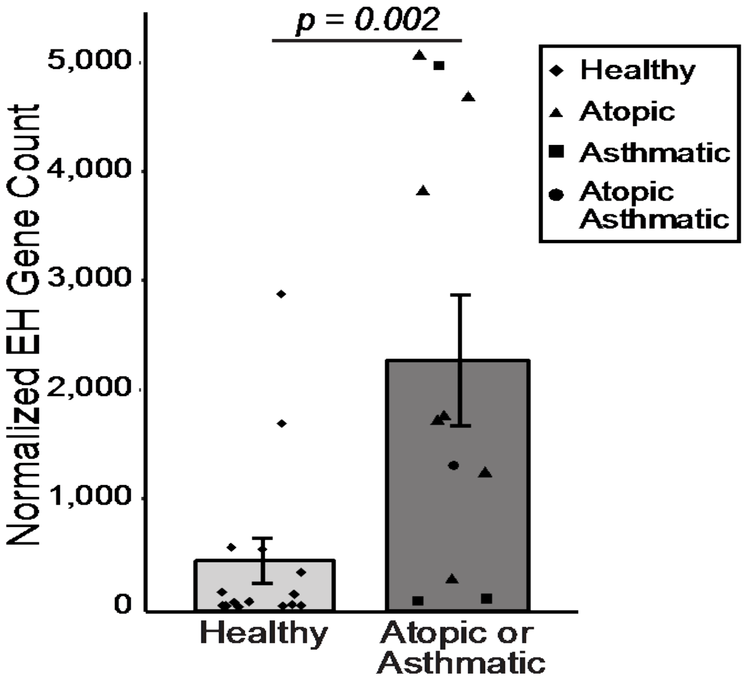
Levan, S. *et al*, Nature Microbiology. 2019

Is the High-risk Neonatal Gut Microbiome Enriched for 12,13 DiHOME Production?

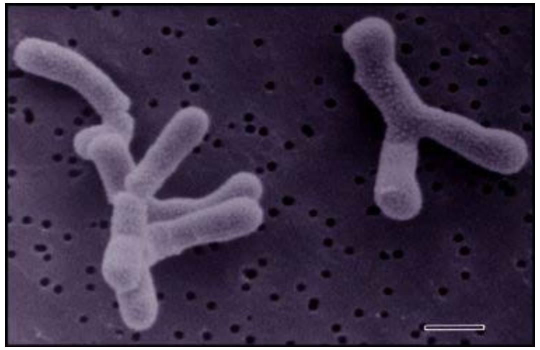




Levan, S. *et al*, Nature Microbiology. 2019

Specific Gut Microbiome Bacterial Strains Encode the Capacity to produce 12,13 DiHOME

Enterococcus faecalis



Bifidobacterium bifidium

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Levan, S. *et al*, Nature Microbiology. 2019

Neonatal Fecal 3EH Copy Number and 12,13 DiHOME Concentration Predicts Childhood Atopy and Asthma

Early-life Gut *Microbial Risk Genes* Identify High-Risk neonates

Microbial-derived Molecular Mechanisms of Early-life Immune Dysfunction that Precede Childhood Disease Development

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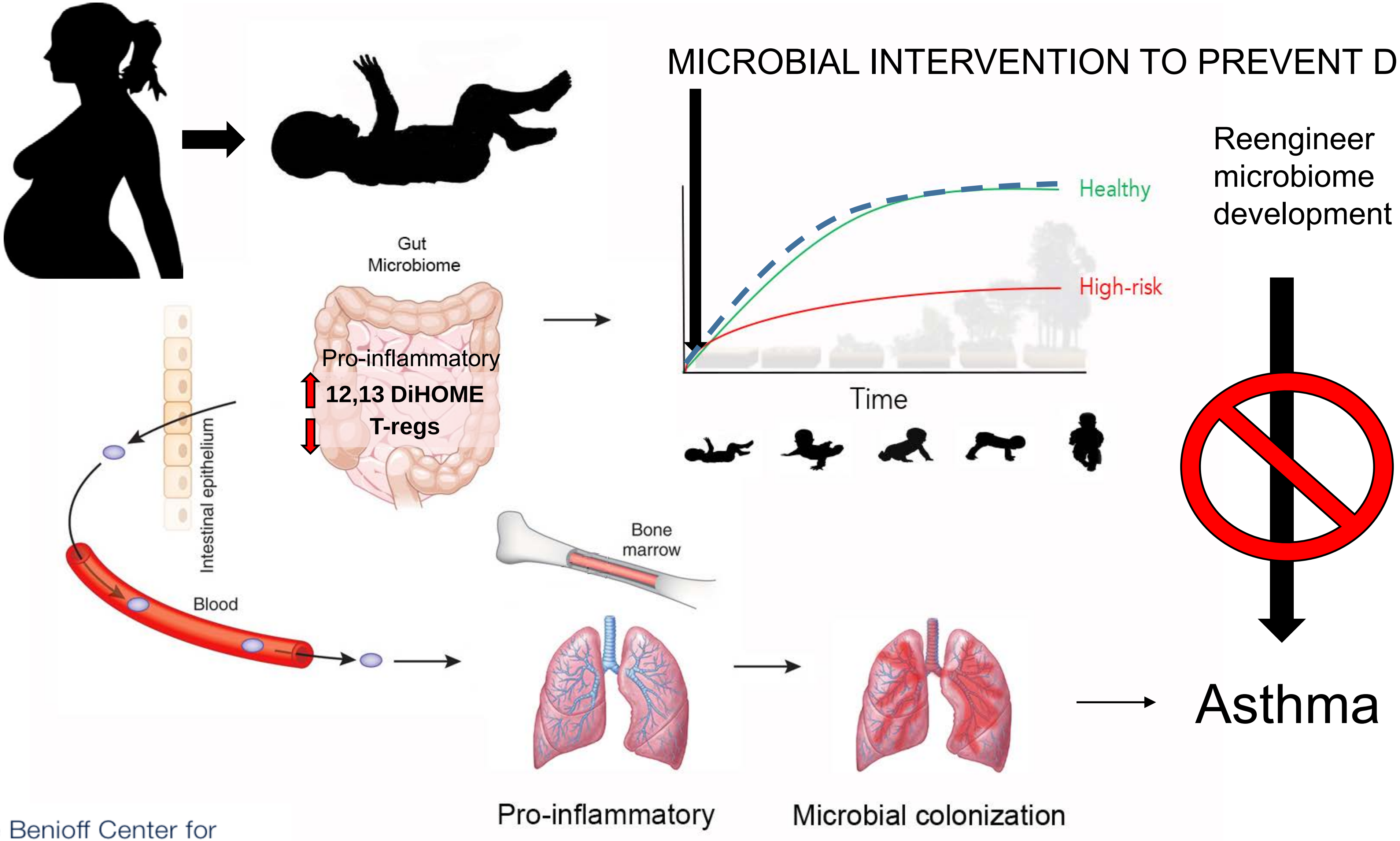
Levan, S. *et al*, Nature Microbiology. 2019

Model for Childhood Atopic Asthma Development

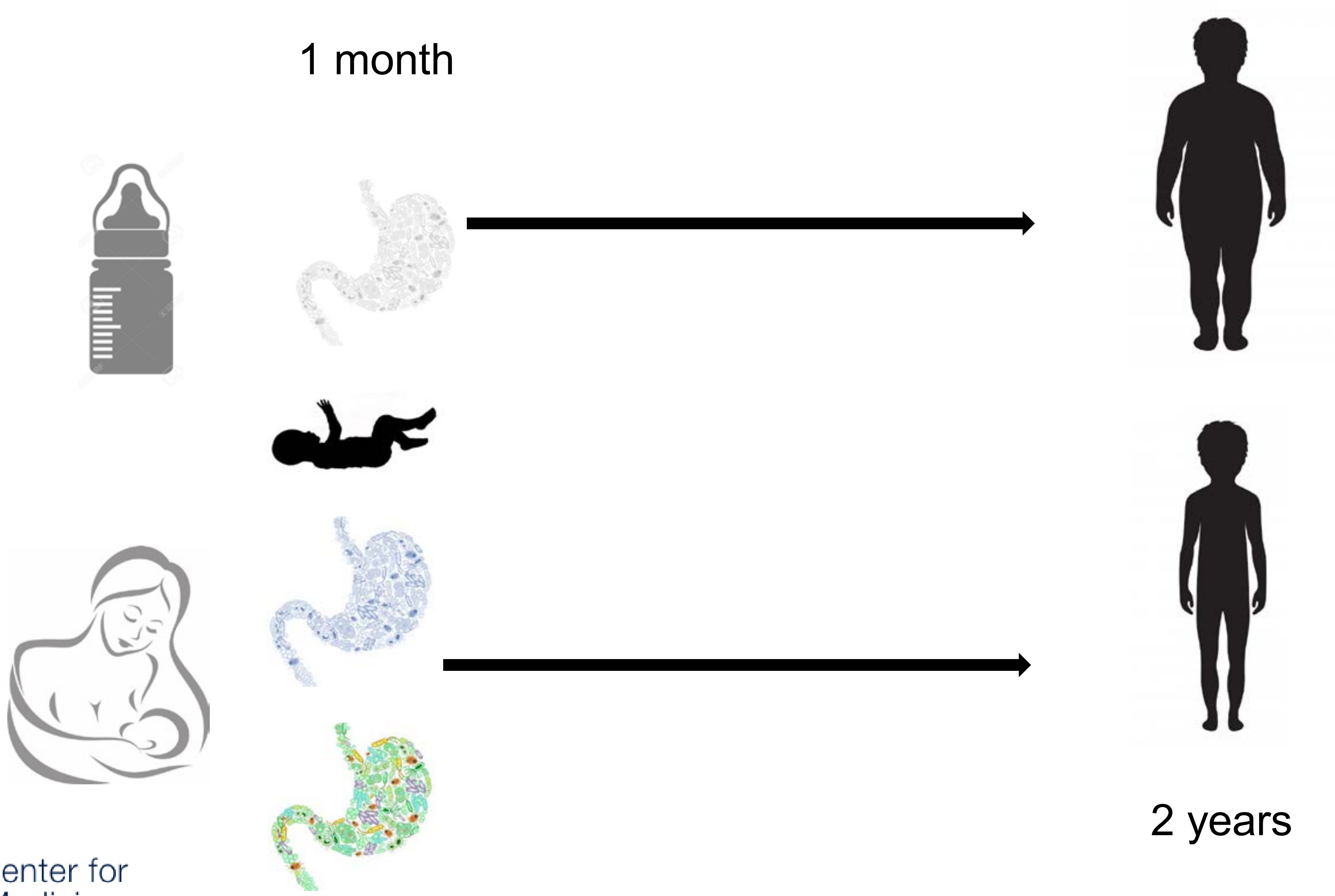


MICROBIAL INTERVENTION TO PREVENT DISEASE

Reengineer
microbiome
development

Asthma

Early-life Gut Microbiota Relates to Childhood Obesity and Overweight Phenotypes at 2 Years



1 month

2 years

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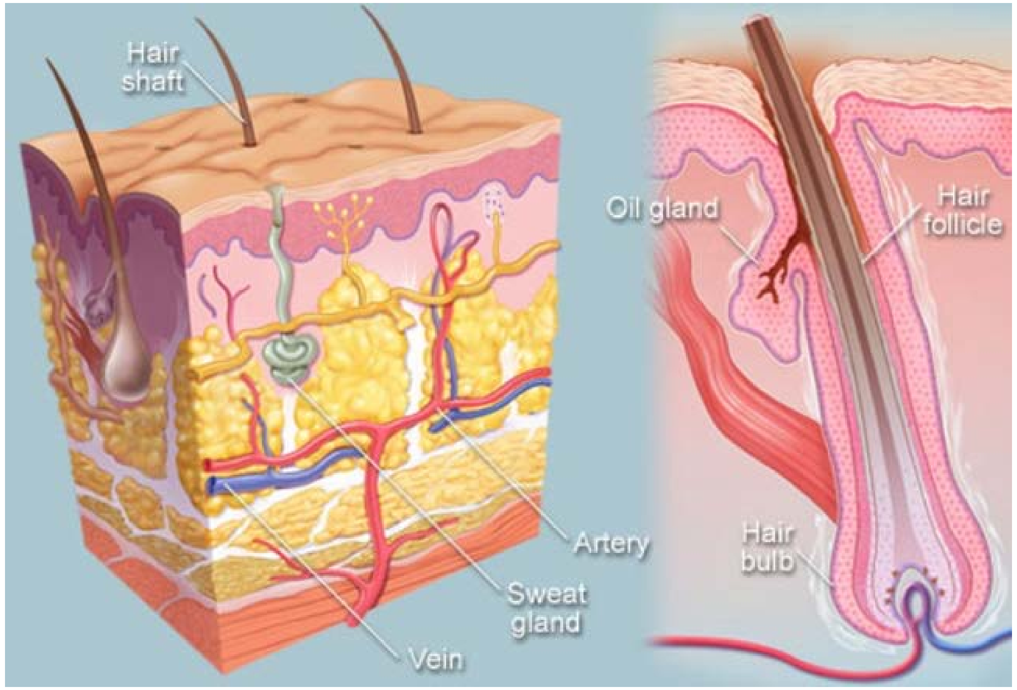
Microbiome Medicine

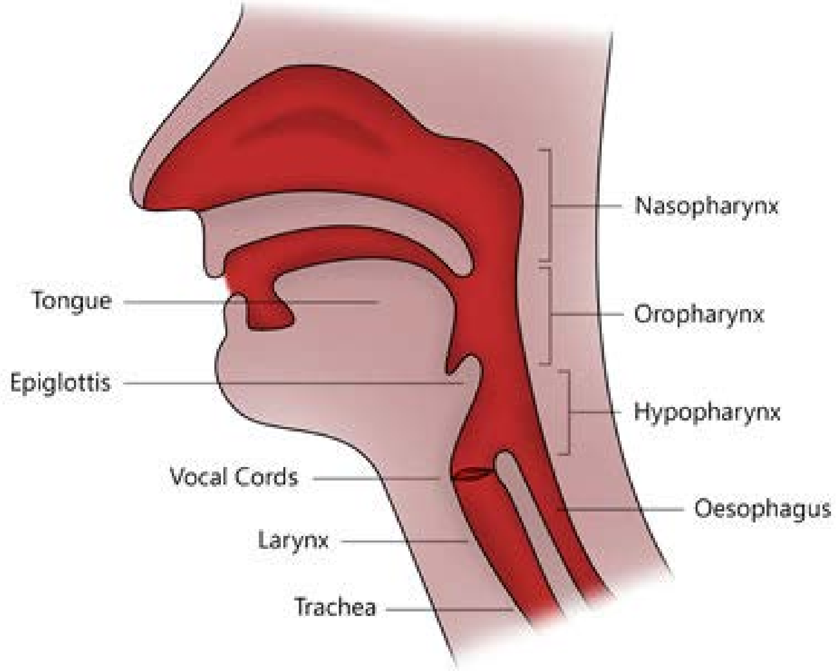
Yong, G. et al. In preparation

Early-life Microbial Colonization Influences Immune Status and Subsequent Microbiome Development



Scharschmidt lab

https://scharschmidtlab.ucsf.edu

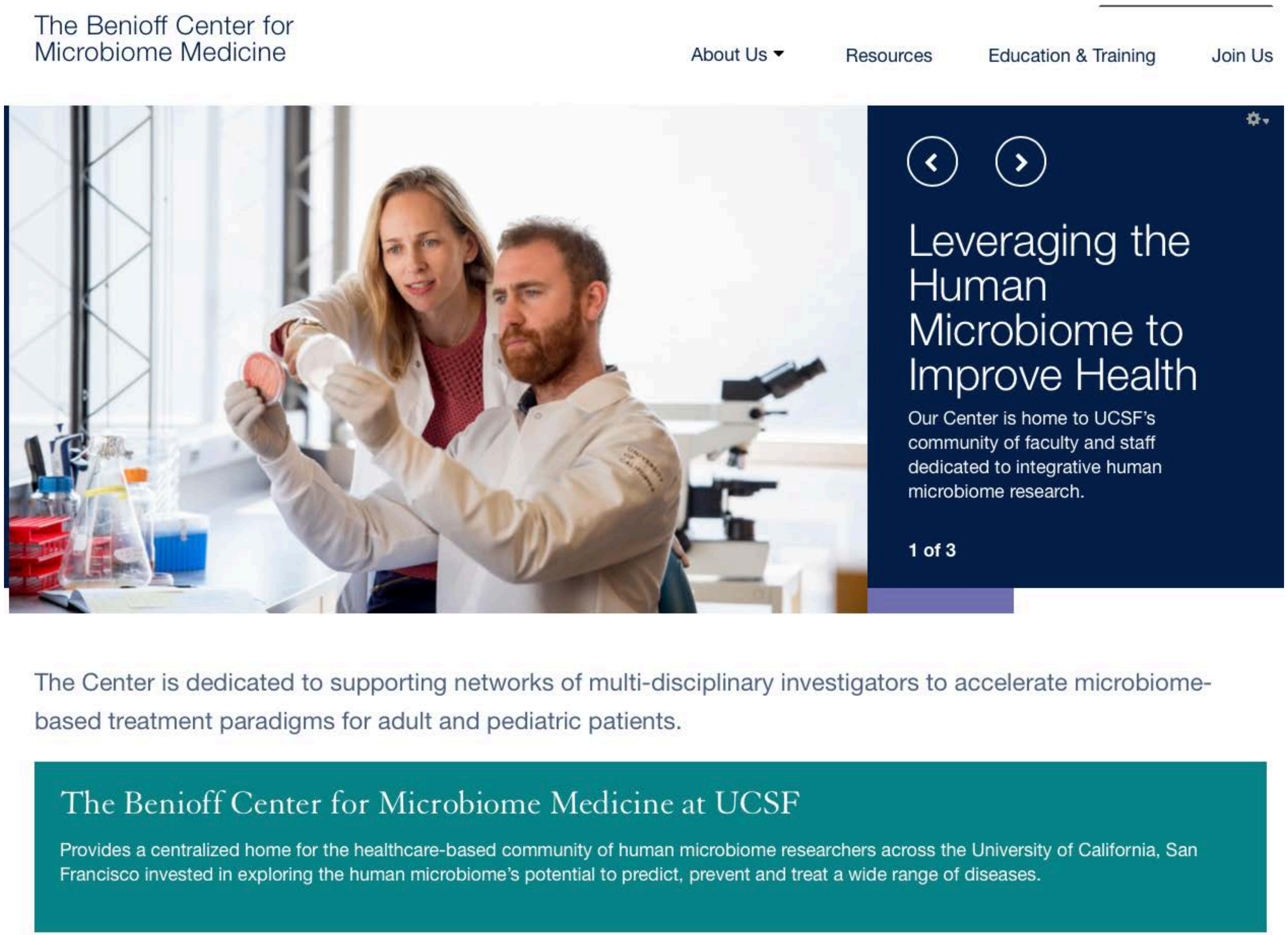


Lynch lab

https://www.slynchlab.com

What Have we Learned and What’s Next?

- Microbiome expands the genetic and functional capacity of its human host
- Human microbiome develops in early life
- Founder populations of gut microbes shape immune function and relate to disease outcomes in childhood
- Microbial-derived metabolites influence critical immune functions necessary for prevention of allergy and asthma
- Early-life microbial colonization relates to childhood health status



Leveraging the Human Microbiome to Improve Health

Our Center is home to UCSF's community of faculty and staff dedicated to integrative human microbiome research.

1 of 3

The Center is dedicated to supporting networks of multi-disciplinary investigators to accelerate microbiome-based treatment paradigms for adult and pediatric patients.

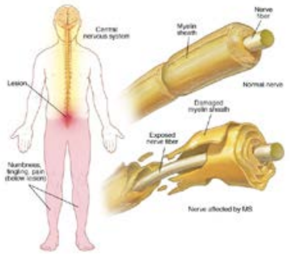
The Benioff Center for Microbiome Medicine at UCSF

Provides a centralized home for the healthcare-based community of human microbiome researchers across the University of California, San Francisco invested in exploring the human microbiome's potential to predict, prevent and treat a wide range of diseases.

Microbiome Research @UCSF

Leveraging healthy oral microbiomes to combat periodontal disease

Gut Microbiome Relates to Multiple Sclerosis



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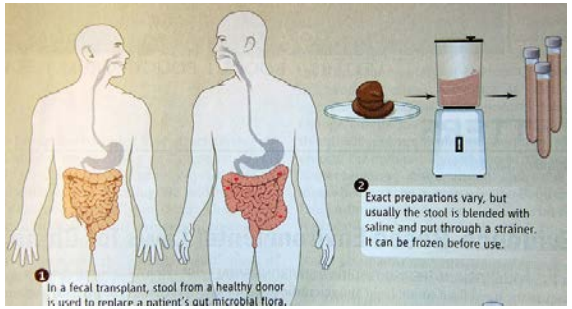
Metagenomic Analysis Permitting Gene-level Associations with Disease

Determining the microbial basis of FMT efficacy



❶ In a fecal transplant, stool from a healthy donor is used to replace a patient's gut microbial flora.

❷ Exact preparations vary, but usually the stool is blended with saline and put through a strainer. It can be frozen before use.

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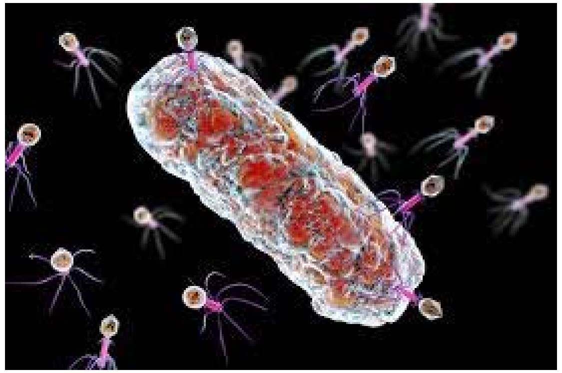
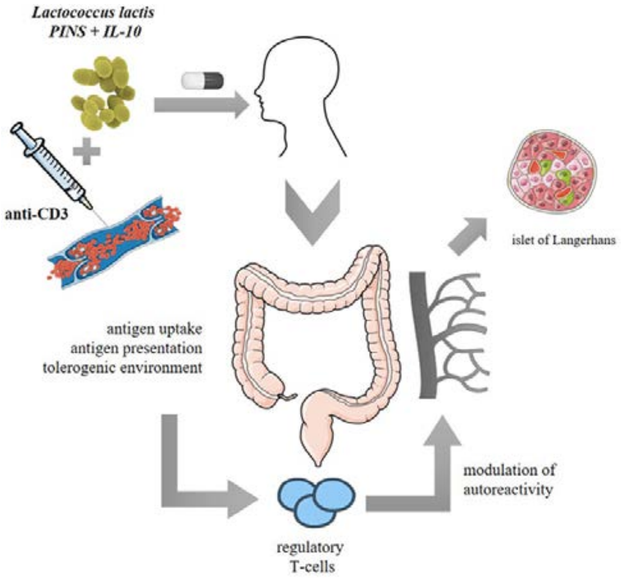
Next-generation Microbiome Therapeutics



PHAGE THERAPY



MICROBIAL GMOS

DIET

LIVE BIOTHERAPEUTICS

PREDICT, PREVENT, TREAT

PREDICT AND PREVENT DISEASE

TAILORED THERAPY

PRECISON MICROBIOME ENGINEERING

ACCELERATE TRANSLATIONAL DISCOVERY