How to Build a Microbiome
Early-life Microbiomes and their Implications for Children's Health

Susan V. Lynch, Ph.D.

Professor of Medicine
Director Benioff Center for Microbiome Medicine
Department of Medicine,
University of California San Francisco, USA.

Image courtesy of The Scientist

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Disclosure

- Co-founder, director and consultant for Siolta Therapeutics Inc.
- Consultant Solarea Bio.

Birth of Microbiome Research

Ann. Rev. Microbiol. 1985. 39:321–46

MEASUREMENT OF IN SITU ACTIVITIES OF NONPHOTOSYNTHETIC MICROORGANISMS IN AQUATIC AND TERRESTRIAL HABITATS

James T. Staley

Department of Microbiology and Immunology, University of Washington, Seattle, Washington 98195

Allan Konopka

Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907

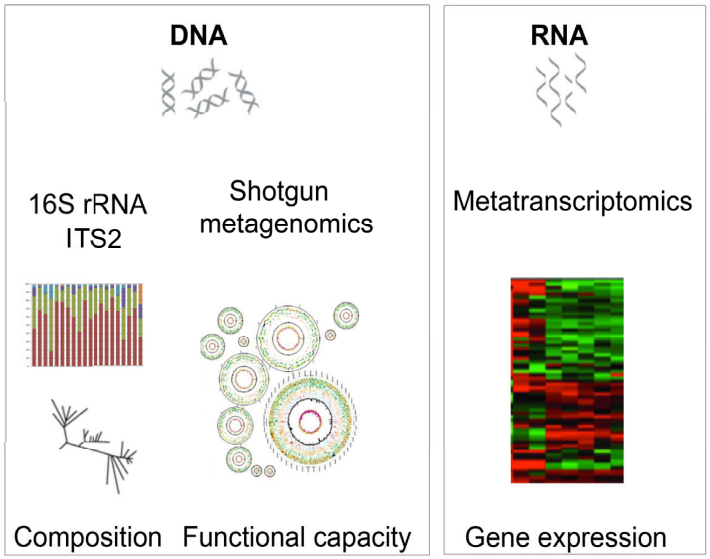
"The Great Plate Count Anomaly"

≠

100 %

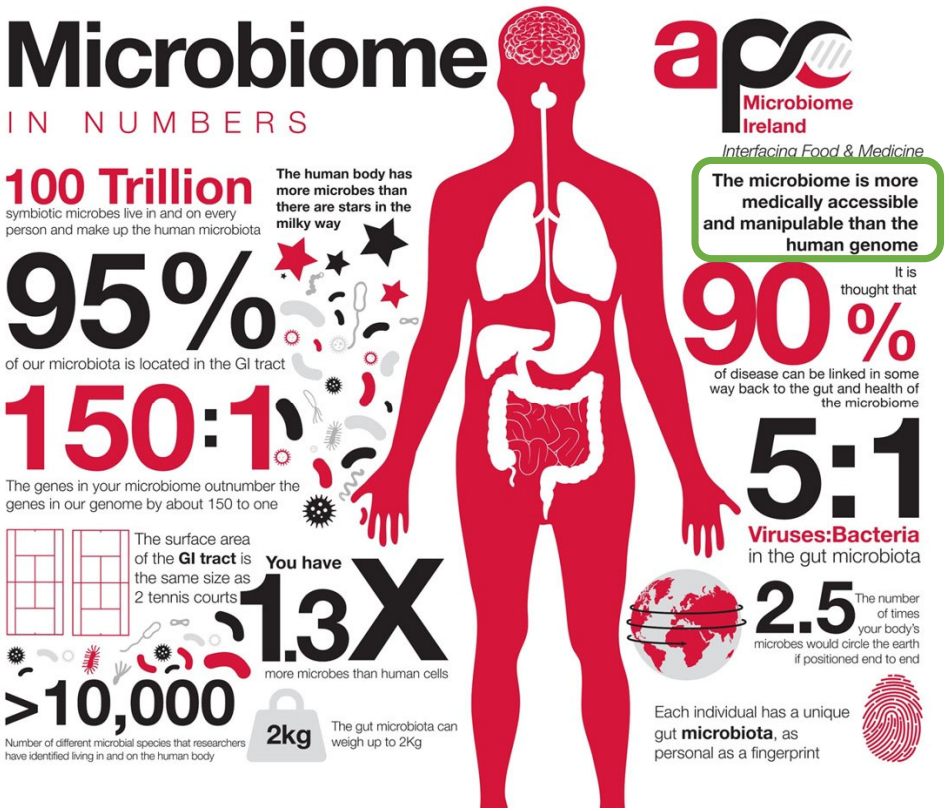
0.001 – 1 %

Culture-based Studies do not Reflect the True Diversity of Microorganisms



Sequence-based analyses

Humans are Superorganisms



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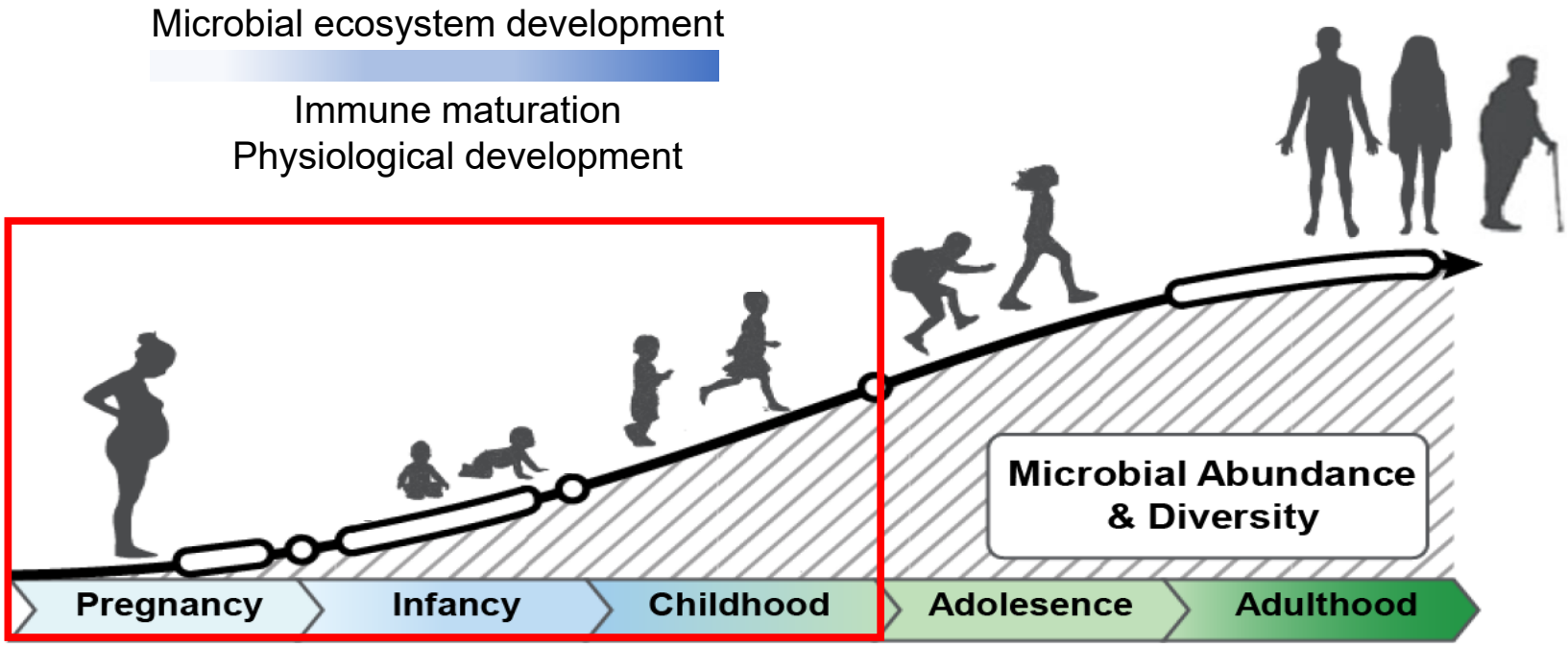
Gut Microbiome Evolves Over Lifespans



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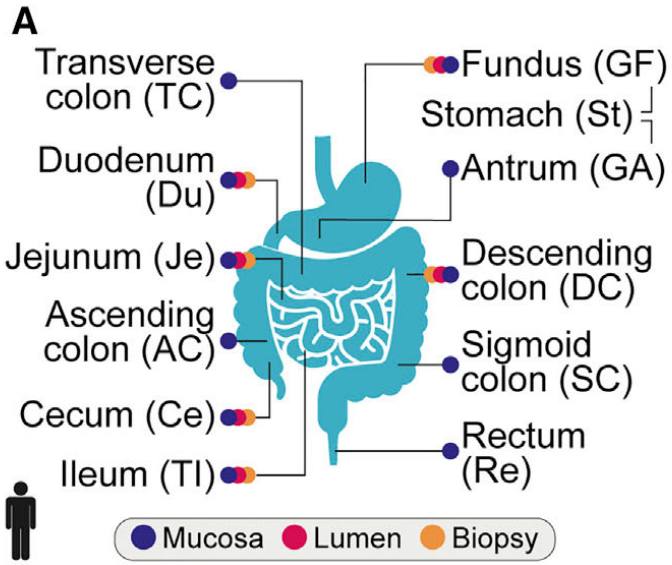
Adapted from: Environmental Chemicals, the Human Microbiome, and Health Risk: A Research Strategy. National Academy of Science and Engineering Report Dec 2017

Microbiome is Spatially Organized in the Gastrointestinal Tract



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

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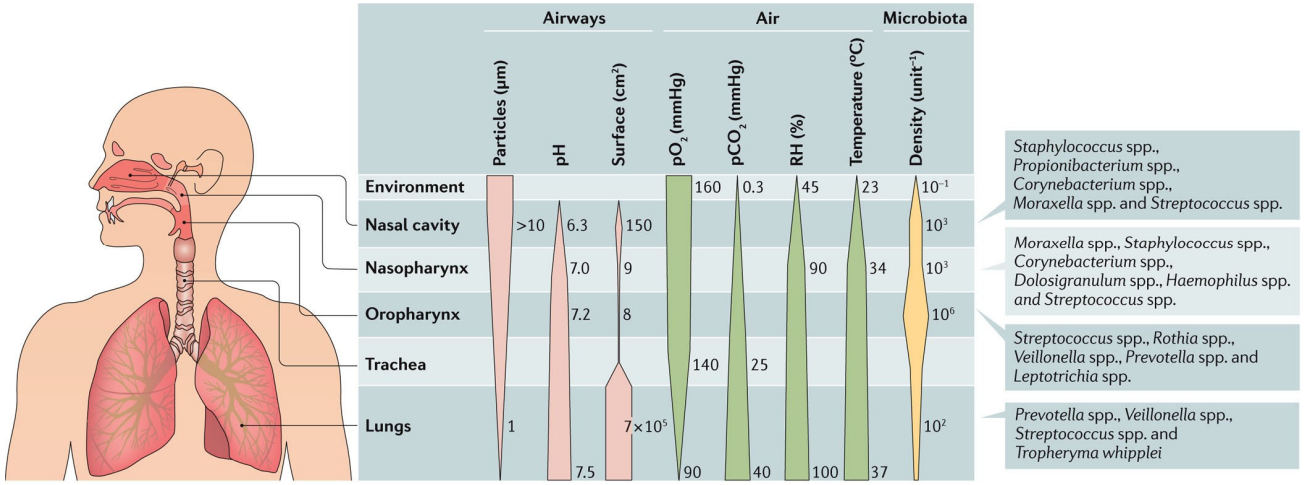
Microbiome is Spatially Organized in the Respiratory Tract and Skin



Man, W., et al., *Nat Rev Microbiol* **15,** 259–270 (2017).

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Intrinsic Factors Shape Microbiomes Across Spatial and Temporal Gradients

Watrous, et al PNAS 2012

Environmental Exposures Shape Microbiomes

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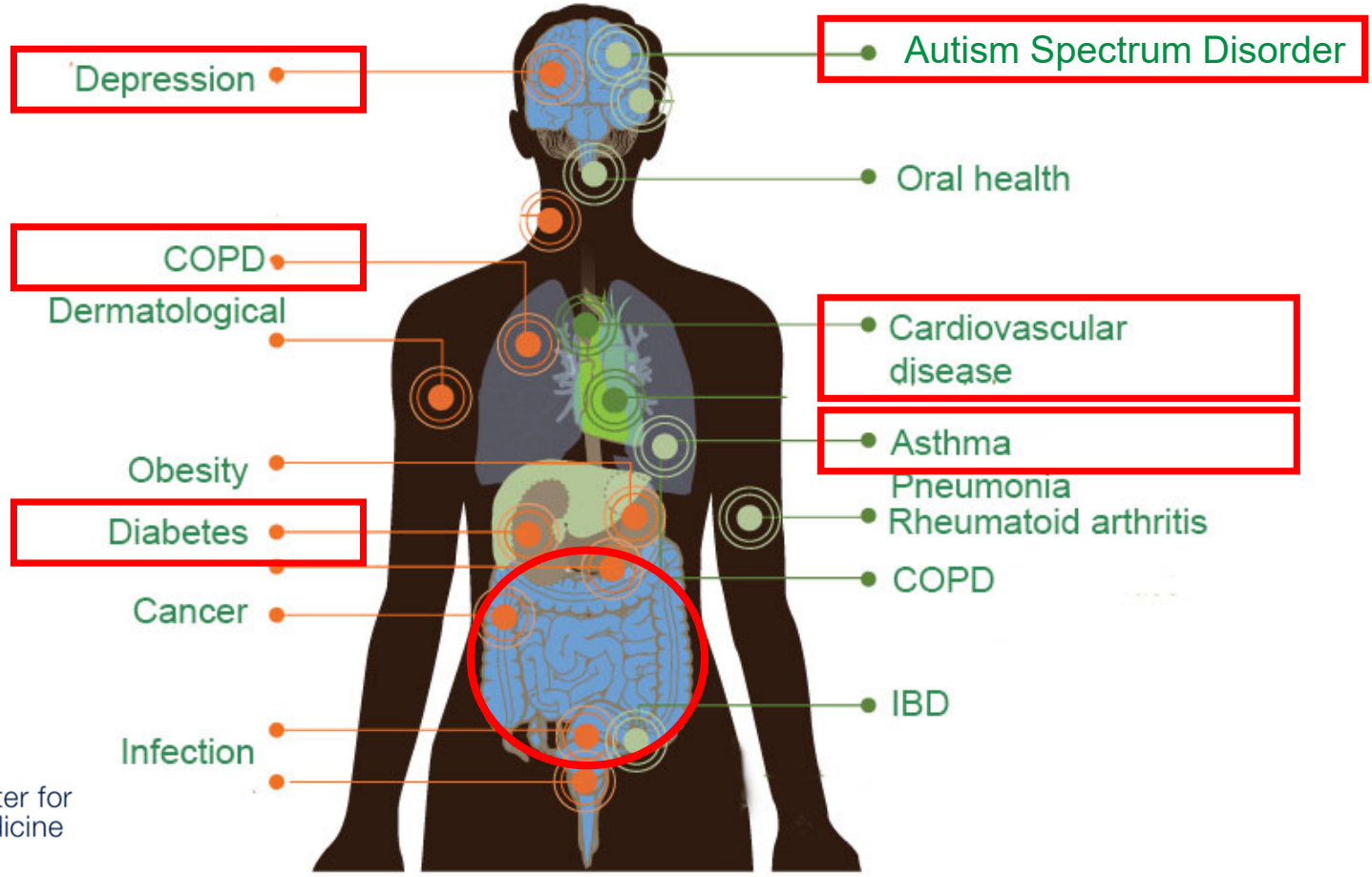
Vermeulen et al. Science. 2020 Jan 24; 367(6476): 392–396. (2020)

At any Stage of Life, the Composition and Activities of the Microbiome at Any Specific Body Habitat are a Reflection of Compounding Intrinsic and Extrinsic Influences

Microbiome Perturbation Associates with Disease



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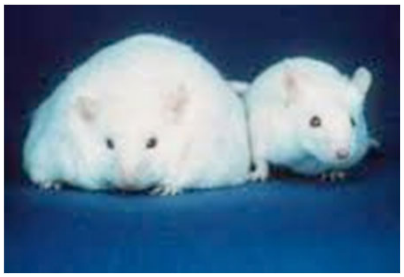
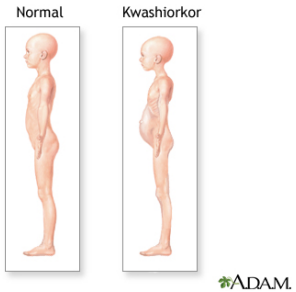
Evidence for the Gut Microbiome as Causal in Disease Development

Obesity



Turnbaugh, P. et al., Nature. 2006 Dec 21;444(7122):1027-31.

Kwashikor

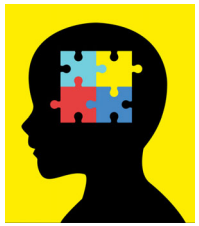


Smith, M.I. *Science.* 2013:Vol. 339 pp. 548-554

Food Allergy

Feehley, T. et al, Nat Med. 2019 Mar;25(3):448-453.

Autism Spectrum Disorder



Sharon, G. Cell. 2019 May 30;177(6):1600-1618.e17.

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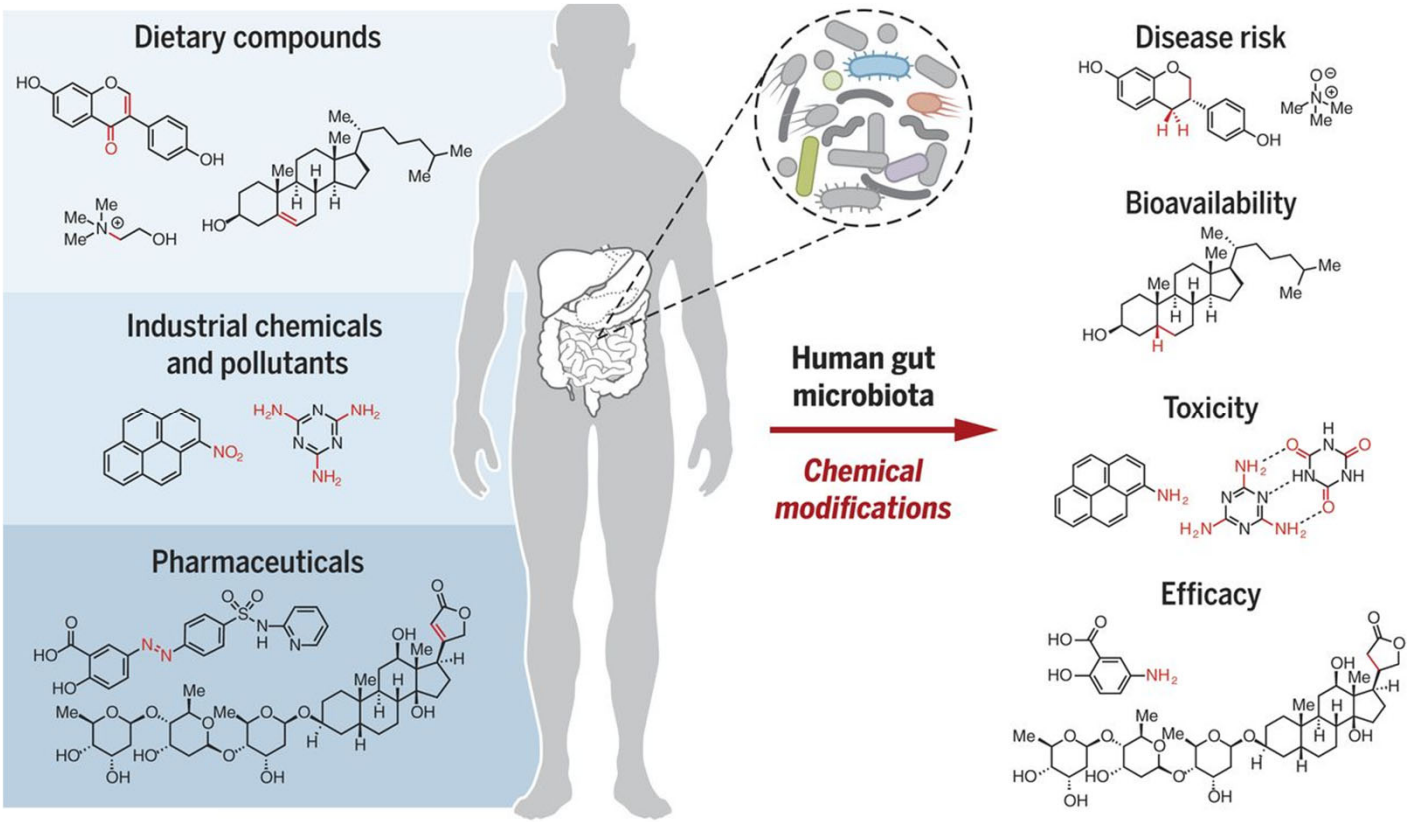
Gut Microbiome is a Major Metabolic Organ



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Koppel, et al *Science* 23 Jun 2017:Vol. 356, Issue 6344, eaag2770

Microbial Metabolic Products Facilitate Microbial-Host Cross-talk

Metabolomics

Bile acids

Bind and activate cell-surface or nuclear receptors, e.g. FXR, GPBAR1 or TGR5

Uric acid

Potent activator of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome

SCFA's

Bind FFA2, FFA3, and GPR109a expressed on epithelium, macrophages and dendritic cells[2]

AHR Ligands

Regulate many aspects of mucosal and systemic immunity, including T-cell and dendritic cell biology

Catecholamines

Augment innate inflammation. Act as neurotransmitters, or systemically as hormones.

Prostaglandins/oyxlipins

Critically important in the regulation of innate and adaptive immunity, as well as epithelium function

Histamine

Modulates immunity, fluid movement in tissues, sleep and gastric acid secretion.

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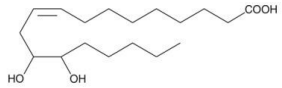
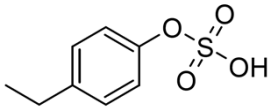
Gut Microbiome Produces Bioactive Metabolites

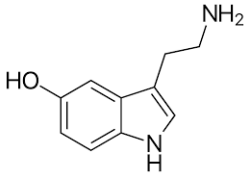


12,13 diHOME

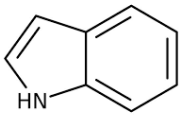
Fujimura, E. et al. Nat Med. 2016



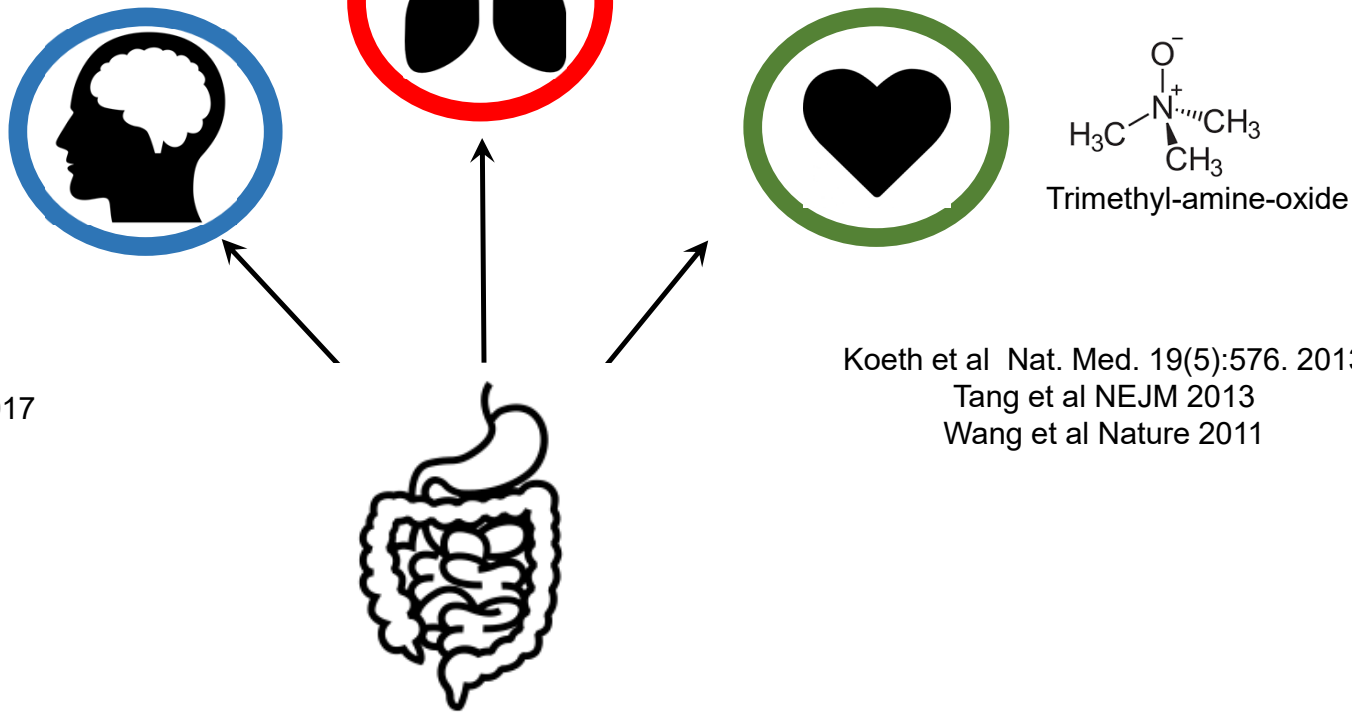
Ethyl-phenyl sulfate



Serotonin



Indole



Trimethyl-amine-oxide

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

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

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Leveraging the Microbiome to Predict, Prevent and Treat Disease

- Leveraging microbiomes for disease prediction
- Mechanistic role in disease development
- Microbiome manipulation to promote health

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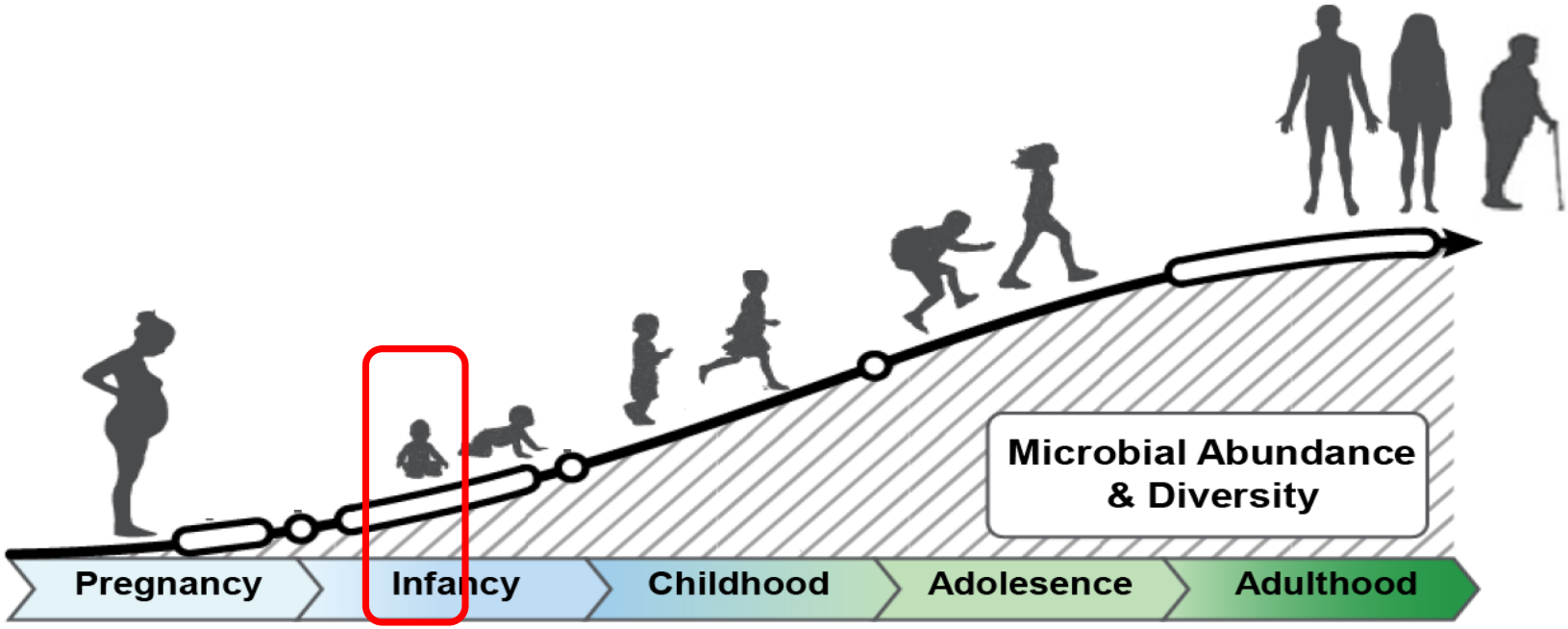
Disease Prediction and Mechanisms

Primary Succession as a Model for Human Microbiome Development



Could the Infant Gut Microbiome Predict Childhood Disease Development?

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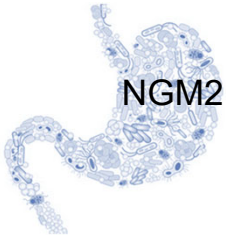
Walker, Lawrence R.; del Moral, Roger. "Primary Succession". *Encyclopedia of Life Sciences*. 2015.

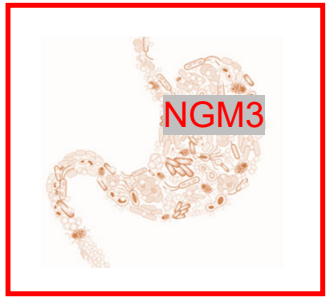
Early-life Gut Microbiome is Associated with Childhood Atopy and Asthma

WHEALS Cohort

16S rRNA; ITS2 (N=130)

Atopy @ 2 years
Asthma @ 4 years





Bacterial depletion
Fungal enrichment
Functionally deficient
Metabolically distinct

Glycolytic
Depleted PUFAs and steroid metabolites

Outcome	NGM1 vs NGM2	NGM 3 vs NGM1	NGM 3 vs NGM2
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

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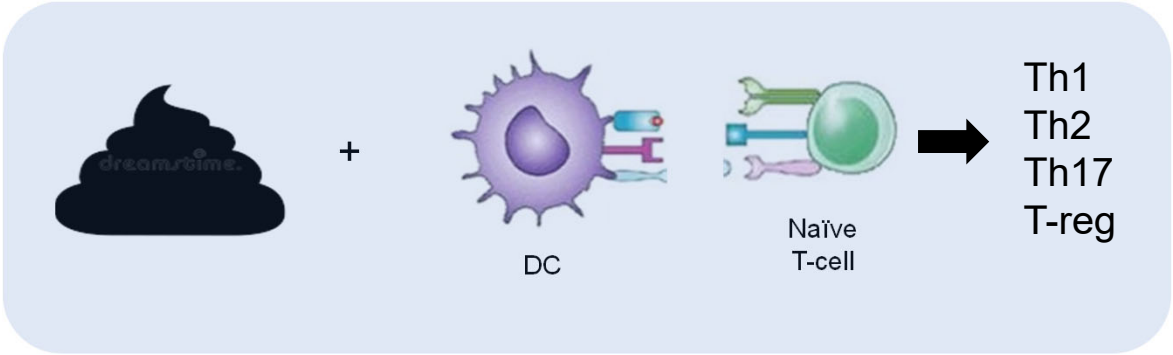
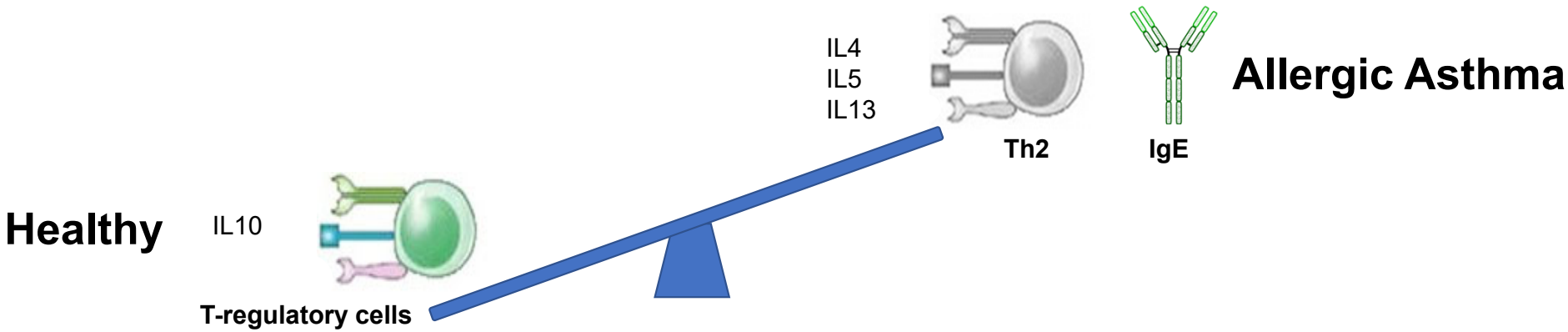
Fujimura, E. et al. *Nature Medicine* 2016

Testing Gut Microbiomes for Pathogenic Potential





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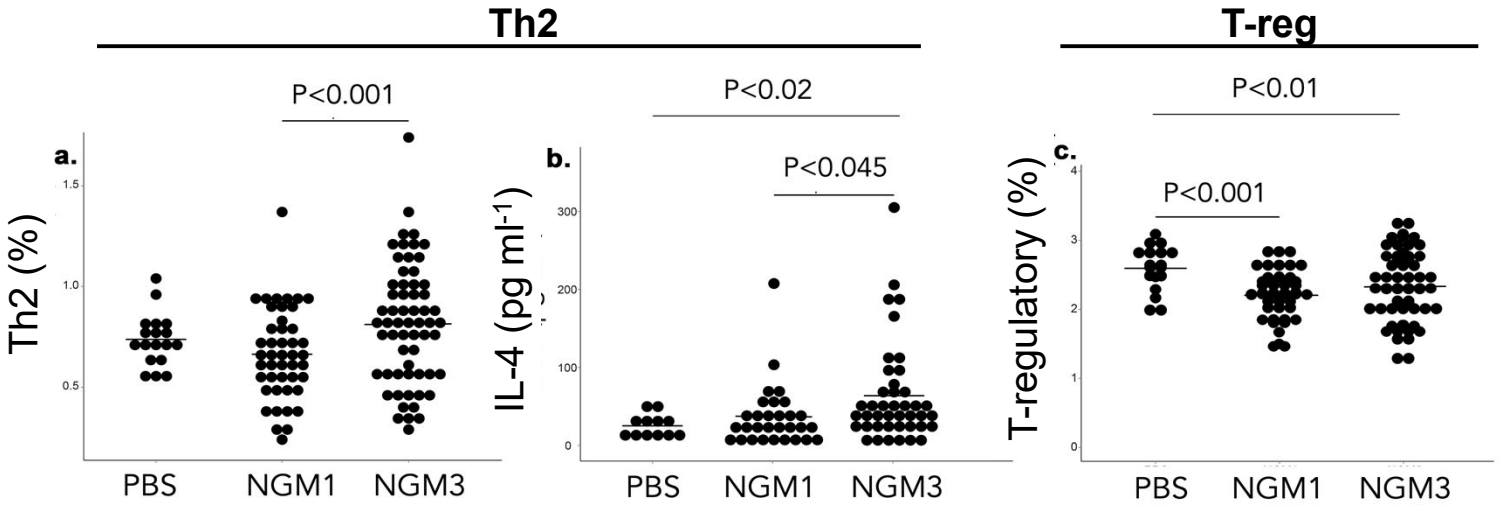
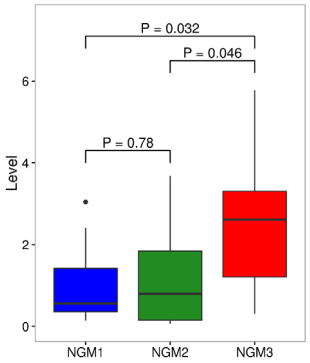
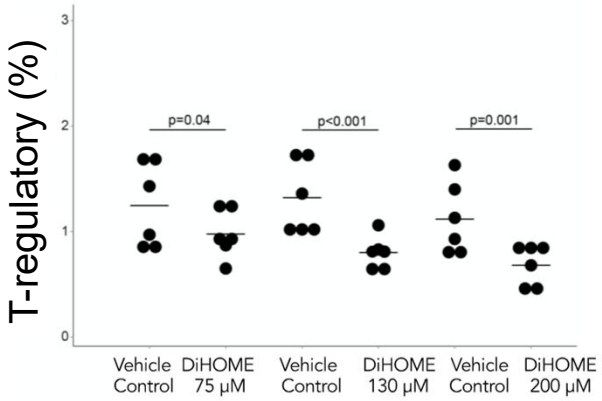
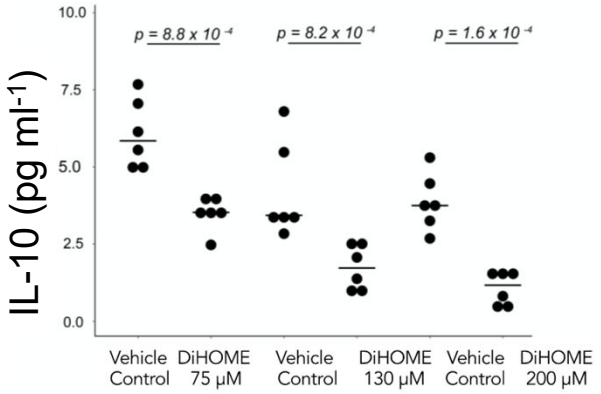
Gut Microbiota Products Influence Immune Function



12,13 DiHOME







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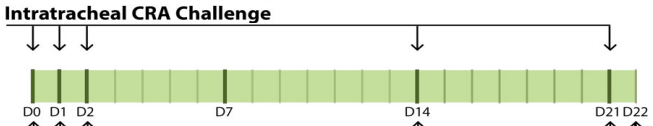
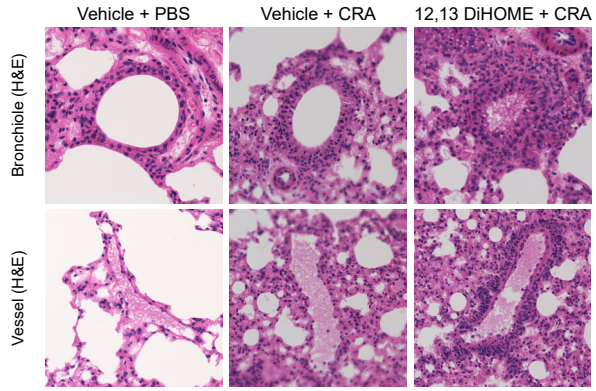
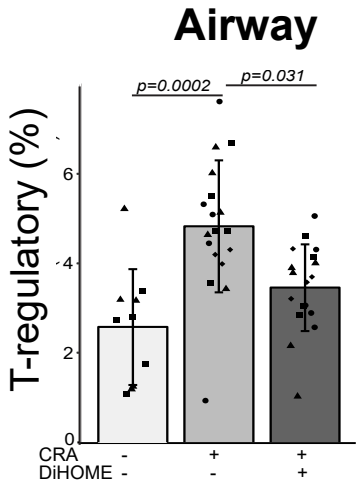
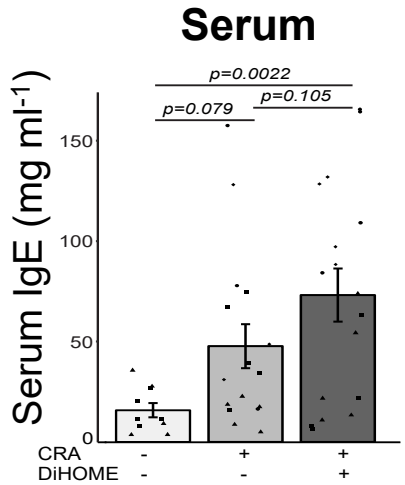
Fujimura, E. et al. *Nature Medicine* 2016

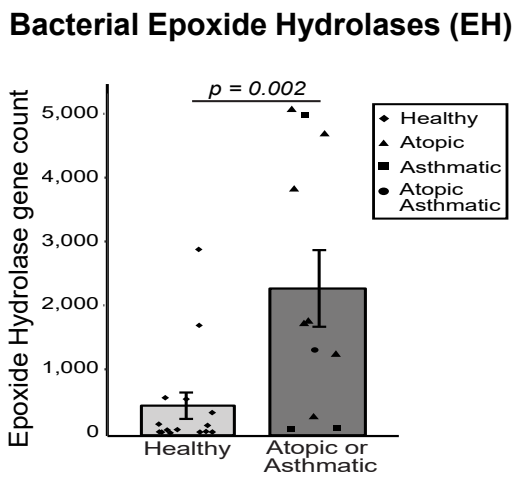
12,13 DiHOME Promotes Airway Allergic Sensitization and Increased Circulating IgE in Mice











Three bacterial EH's produced 12,13 DiHOME

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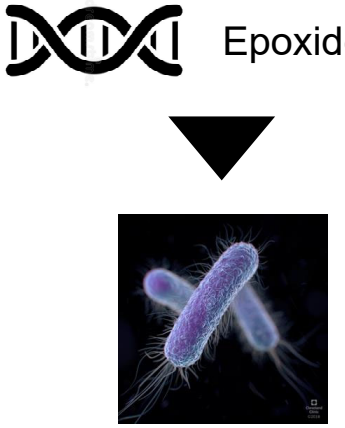
Levan, S. *et al*, Nature Microbiology. 2019

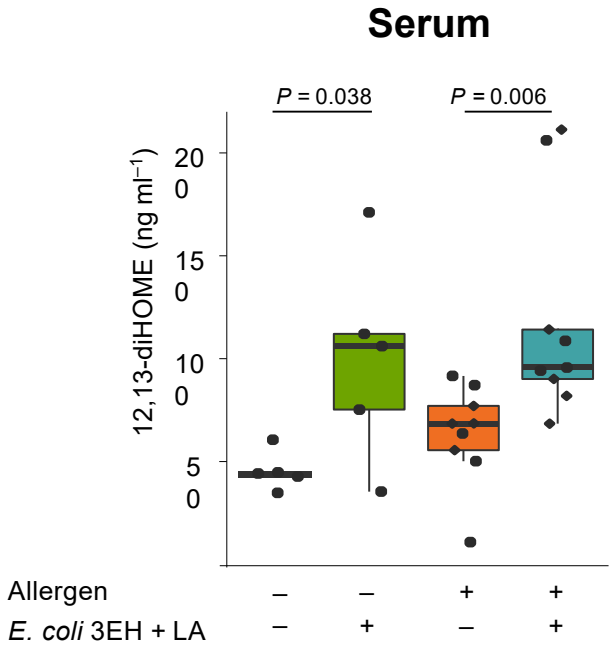
Introduction of Bacterial EH Genes to the Gut Microbiome Exacerbates Airway Allergic Inflammation



Epoxide hydrolase

12,13 DiHOME producing *Escherichia coli*

	I	II	III	IV
Allergen	–	–	+	+
E. coli EH + LA	–	+	–	+



Allergen	–	–	+	+
E. coli 3EH + LA	–	+	–	+

Allergen = Cockroach antigen
EH = *E. coli* encoding bacterial epoxide hydrolase genes
LA = Linoleic acid

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Levan et al. 2019 Nat. Microbiol 2019 Nov;4(11):1851-1861.

Gut Microbiome as a Predictor of Health

nature COMMUNICATIONS

Gut microbiome development differs in healthy and high-risk for atopy infants[2]

nature
International weekly journal of science

Associations between early life gut microbial taxonomy and the development of islet autoimmunity or type 1 diabetes[3]

nature
International weekly journal of science

Bacterial pathways for short-chain fatty acid biosynthesis were depleted in the early life gut microbiome of subjects who developed T1D[4]

Unpublished

Precocious Infant Gut Microbiome Reprograms Enterocyte Function and Promotes Childhood Obesity Risk.

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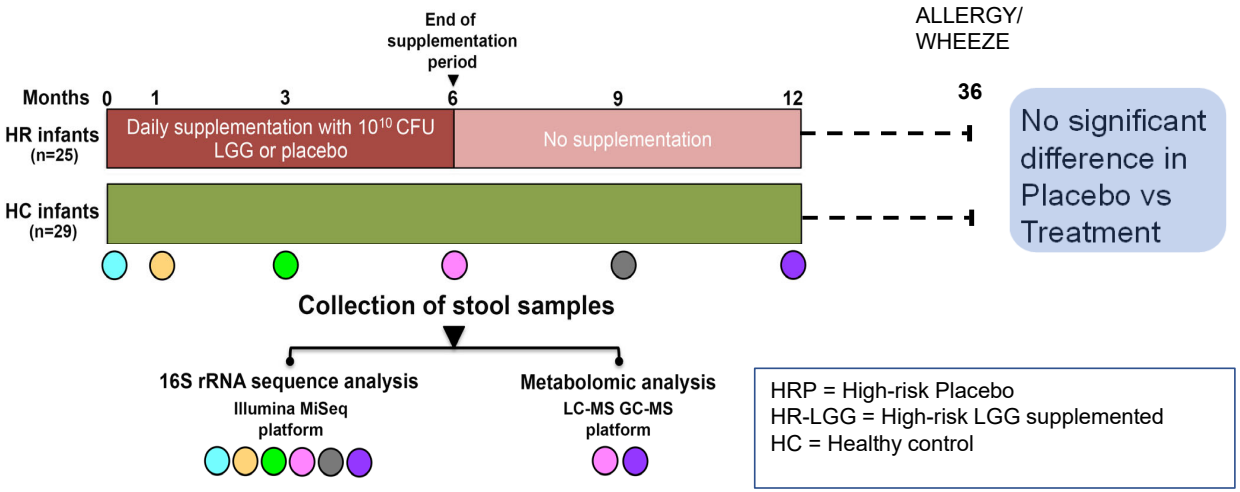
[1] Durack et al. 2018 Nat. Commun. 2018 Feb 16;9(1):707. [2] Vataneb et al., Nature. 2018; 562(7728): 589–594. [3] Stewart et al., Nature. 2018; 562(7728): 583–588.

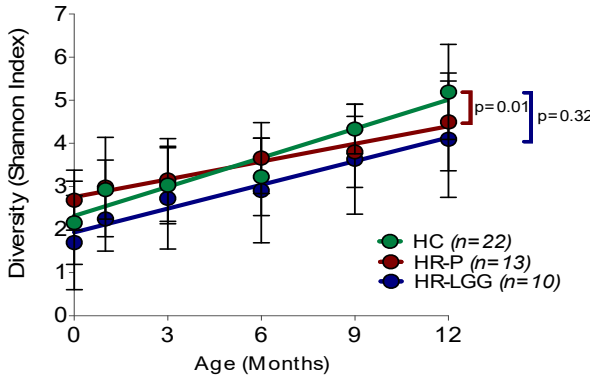
Microbiome manipulation to promote health

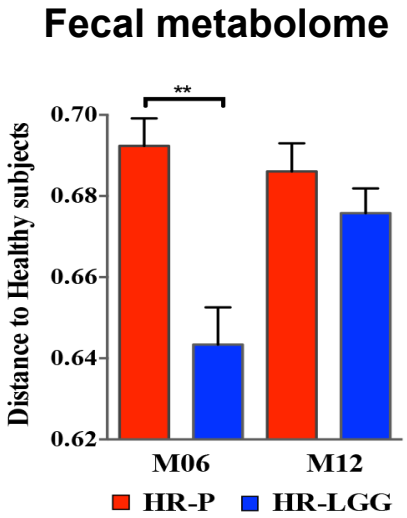
Early-life Microbial Supplementation to Prevent Childhood Allergic Disease



No significant difference in Placebo vs Treatment

HRP = High-risk Placebo
HR-LGG = High-risk LGG supplemented
HC = Healthy control





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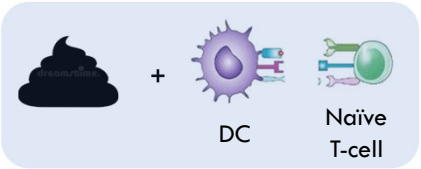
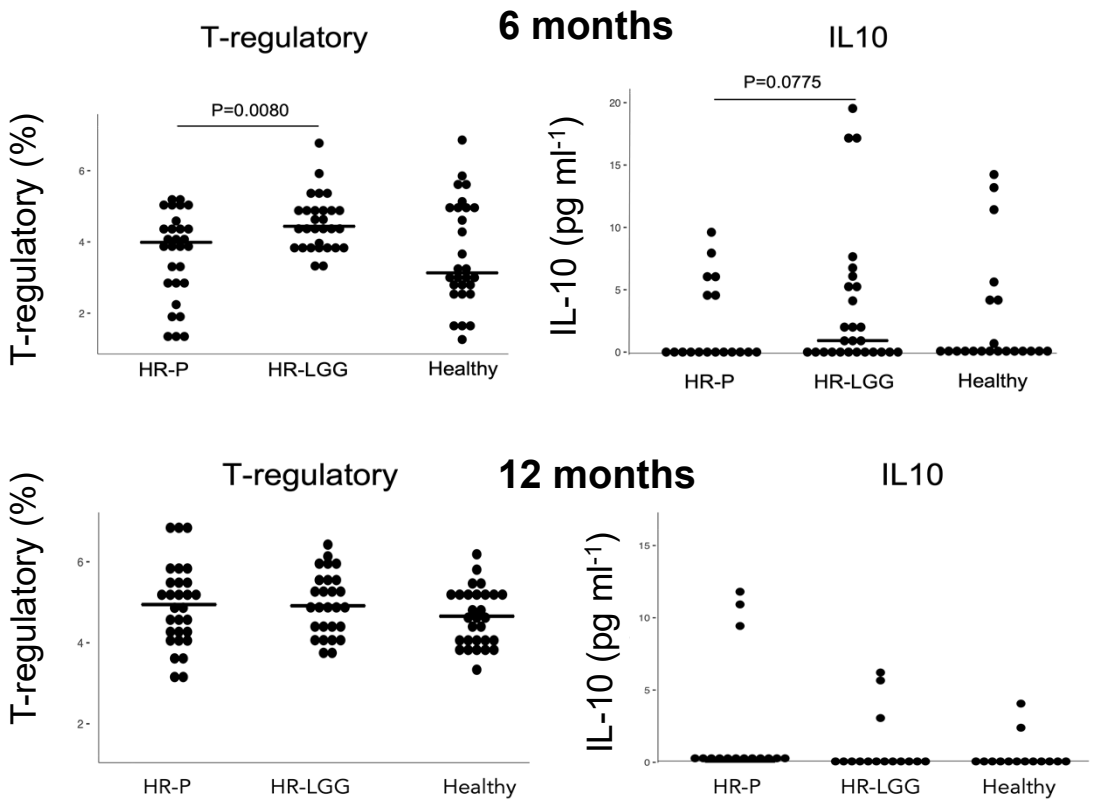
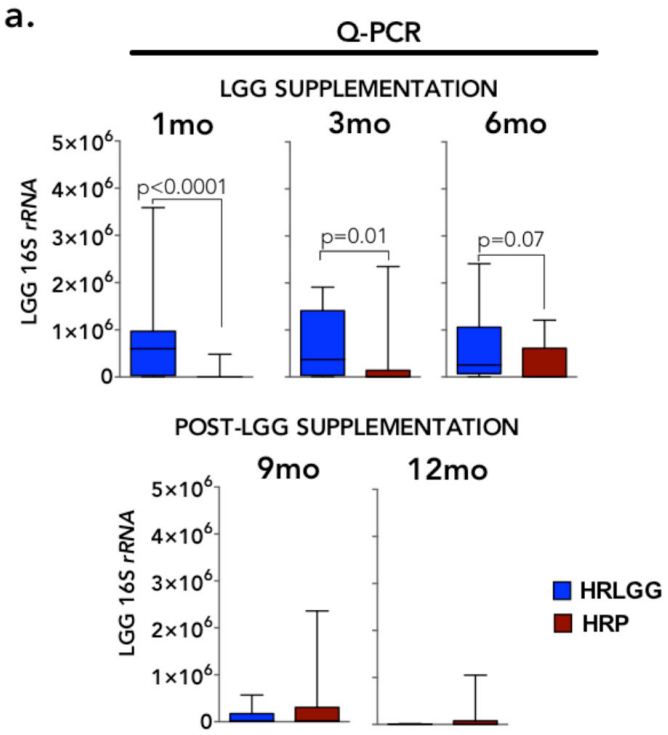
Early-life Gut Microbial Products Influence Immune Function







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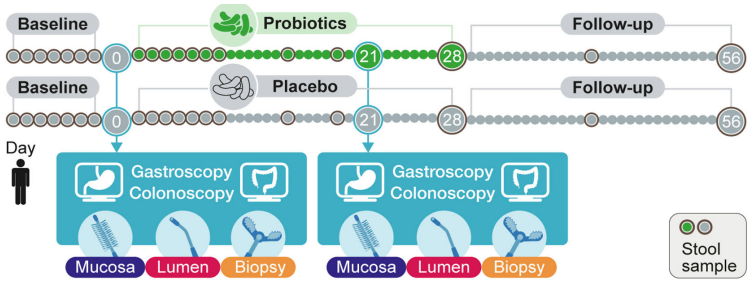
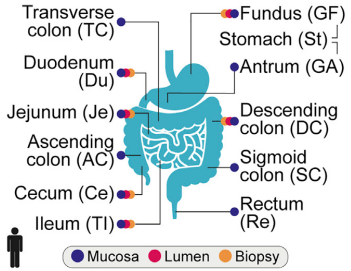
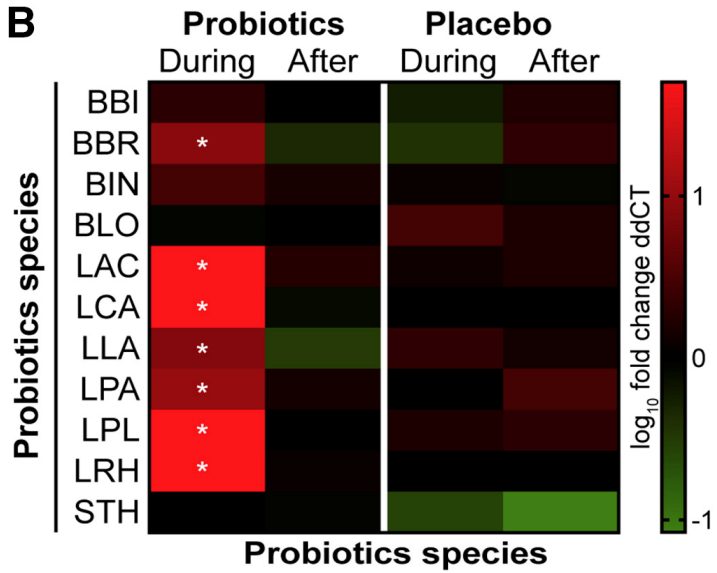
Durack et al. 2018 Nat. Commun. 2018 Feb 16;9(1):707

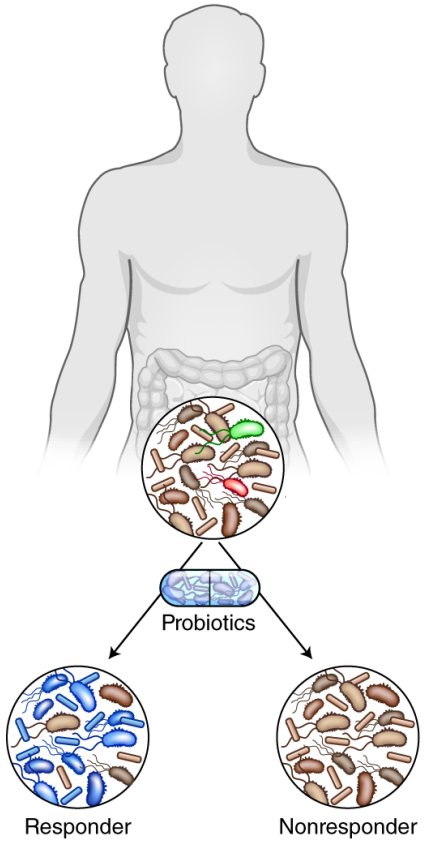
Empiric Probiotic Supplementation May be Limited in Universally and Persistently Impacting the Gut Mucosa







Lactobacillus acidophilus (LAC)
Lactobacillus casei (LCA)
Lactobacillus casei sbsp. *paracasei* (LPA)
Lactobacillus plantarum (LPL)
Lactobacillus rhamnosus (LRH)
Bifidobacterium longum (BLO)
Bifidobacterium bifidum (BBI)
Bifidobacterium breve (BBR)
Bifidobacterium longum sbsp. *infantis* (BIN)
Lactococcus lactis (LLA)
Streptococcus thermophilus (STH)

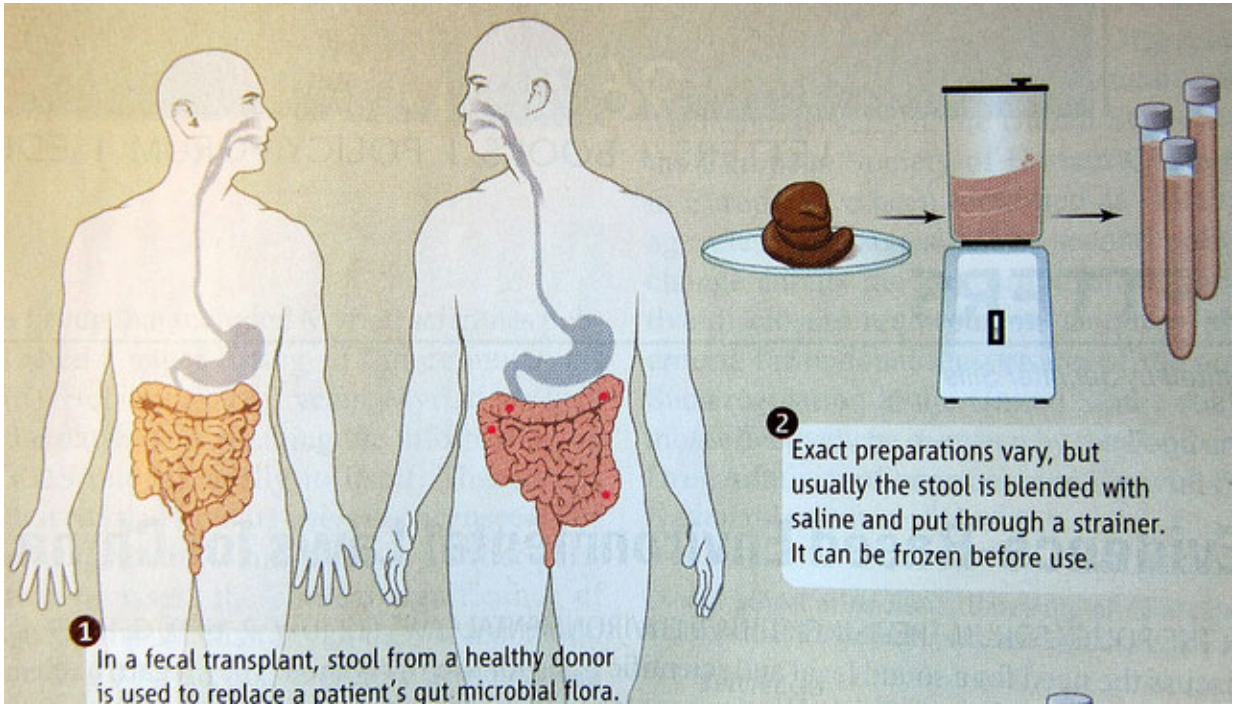


Zmora et al., 2018, Cell *174*, 1388–1405
September 6, 2018 © 2018 Elsevier Inc.
https://doi.org/10.1016/j.cell.2018.08.041

Need for Rationally Designed Microbial Cellular Therapeutics

Rackaityte, E. et al, *Nature Medicine* **volume 24**, pages1642–1644 (2018)

Fecal Microbial Transplant

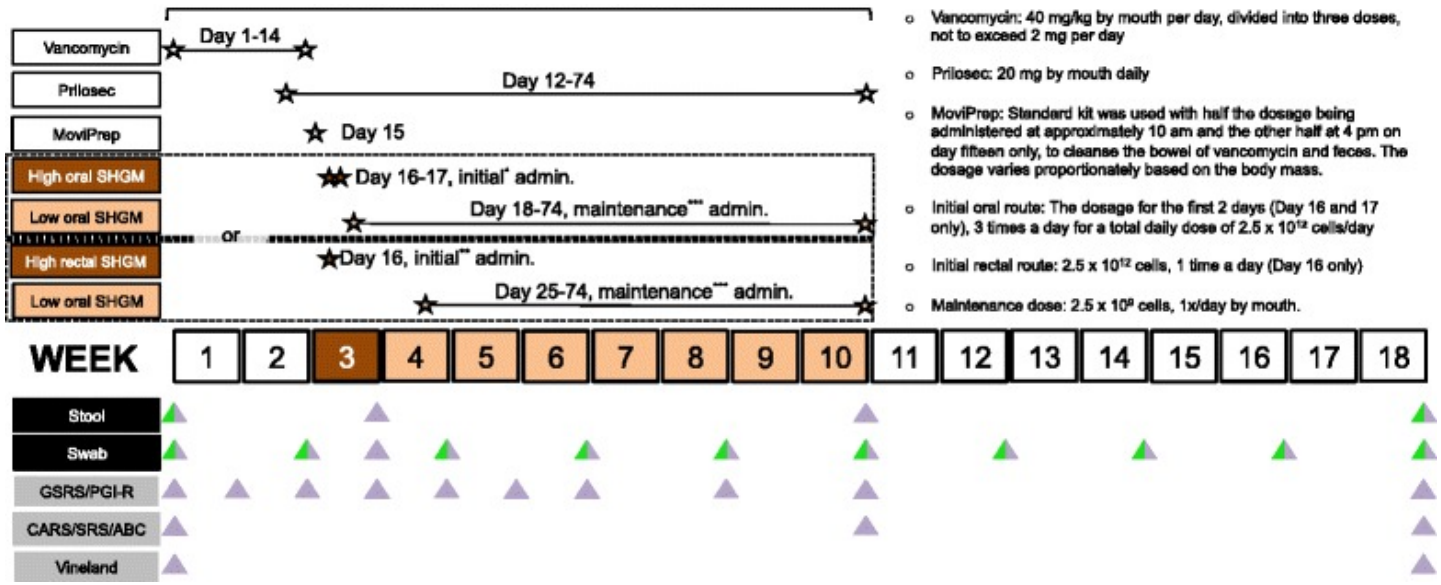


***Clostridium difficile* Infection**

Autism Spectrum Disorder

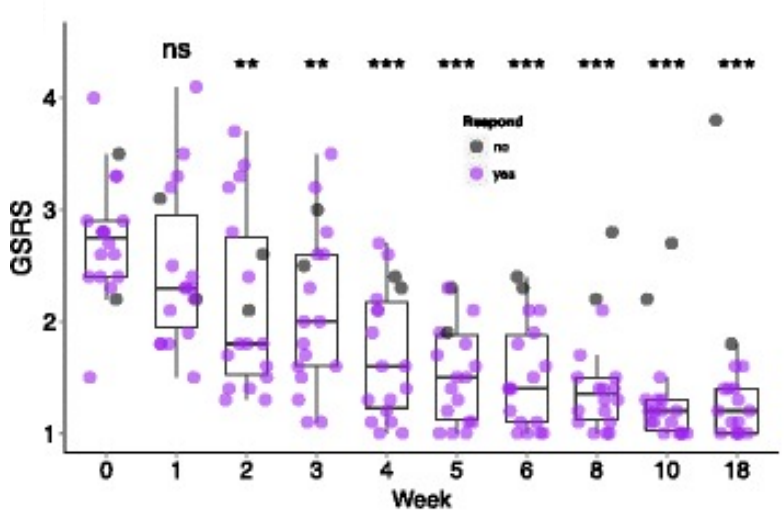
Ulcerative Colitis

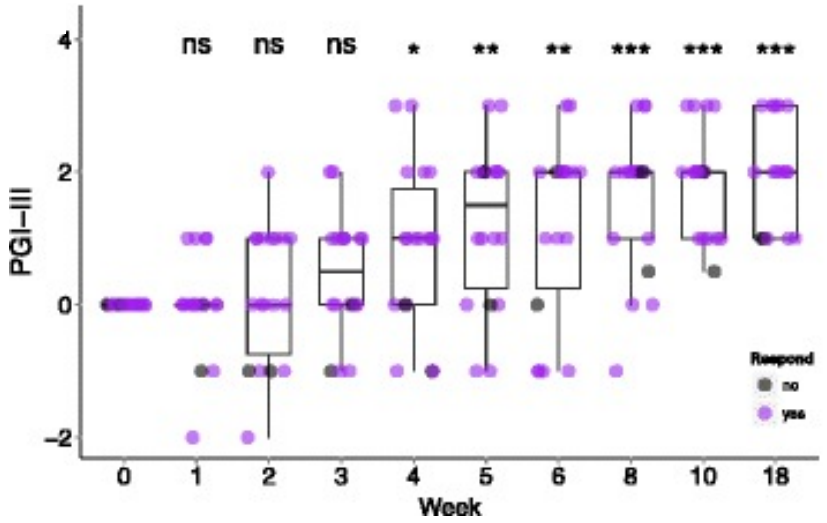
10-week Pediatric Microbiota Transfer Therapy Study Design



Dae-Wook Kang, Microbiome. 2017; 5: 10.v

GI- and ASD-related Symptoms Improve with FMT



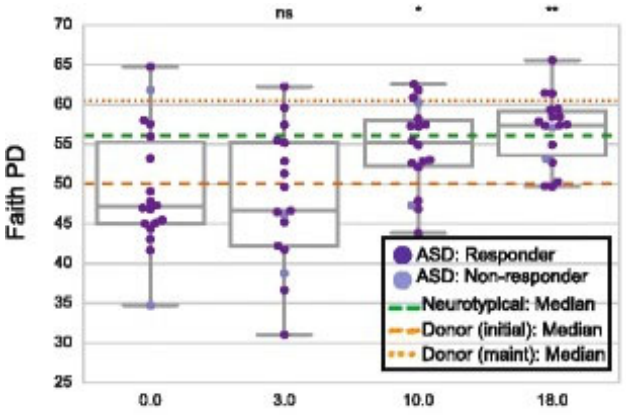


GSRS=Gastrointestinal Symptom Rating Score

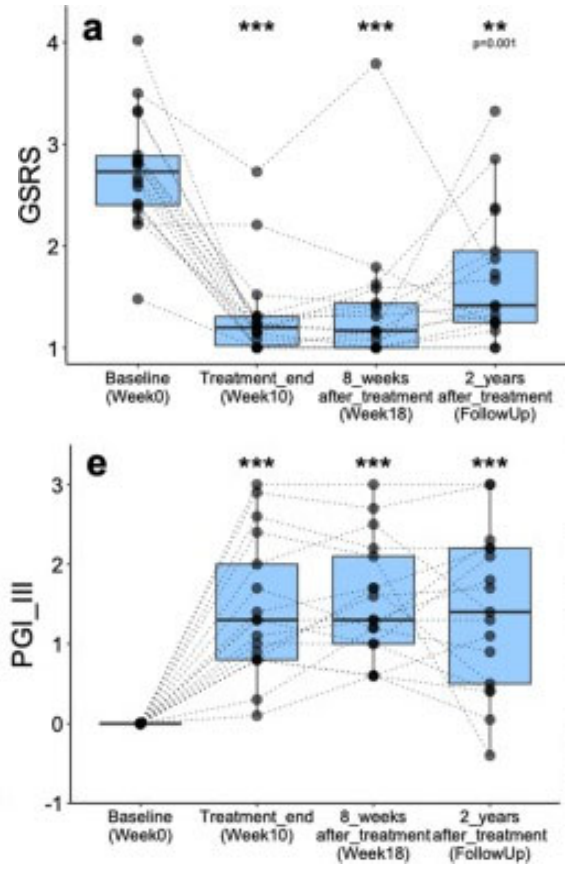
PGI-III=Parent Global Impressions Score

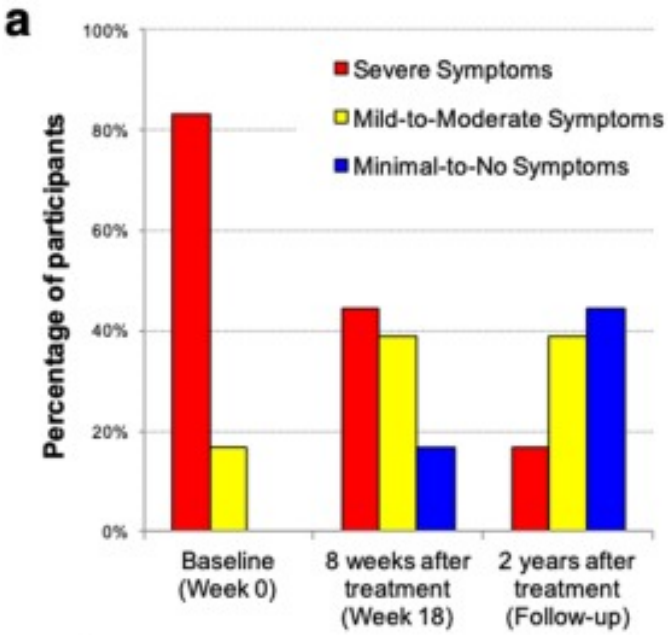
Dae-Wook Kang, Microbiome. 2017; 5: 10.

Fecal Microbiota Changes Correspond with Sustained Clinical Improvement



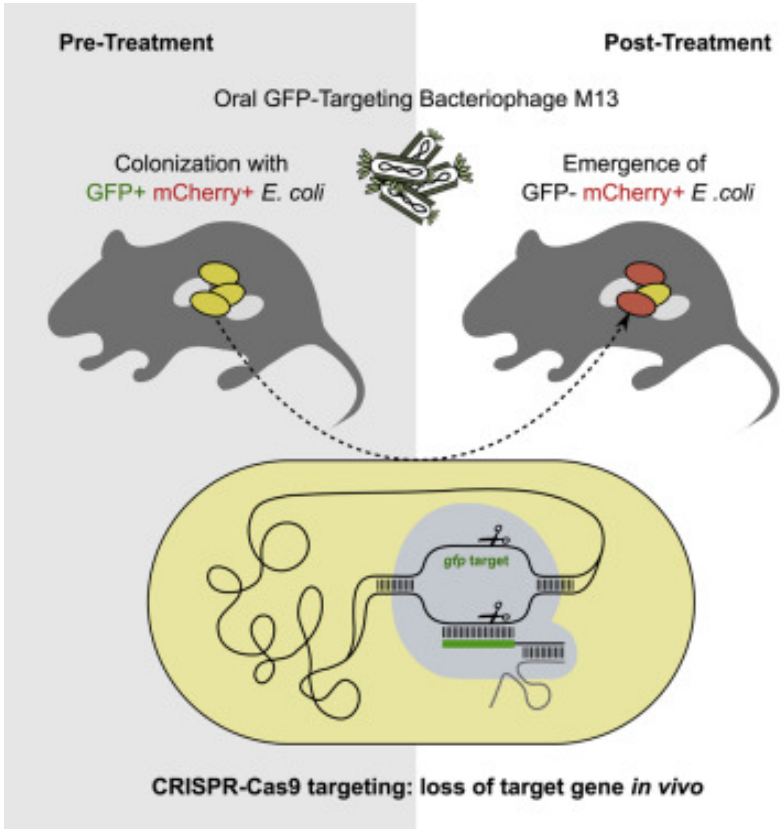
Dae-Wook Kang, Microbiome. 2017; 5: 10.





Dae-Wook Kang et al, Sci Rep. 2019 Apr 9;9(1):5821.

Precision Microbiome Engineering



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Lam *et al, Cell Reports* 2021 37DOI: (10.1016/j.celrep.2021.109930)

Summary

- Early life represents a key period in human microbiome development
- Early life microbiome can predict childhood disease or adverse pregnancy outcomes
- Microbiome manipulation strategies may offer opportunities to develop novel interventions for a range of diseases.

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