제12차 천식연구회 · COPD연구회 공동심포지엄

Microbiome and Asthma

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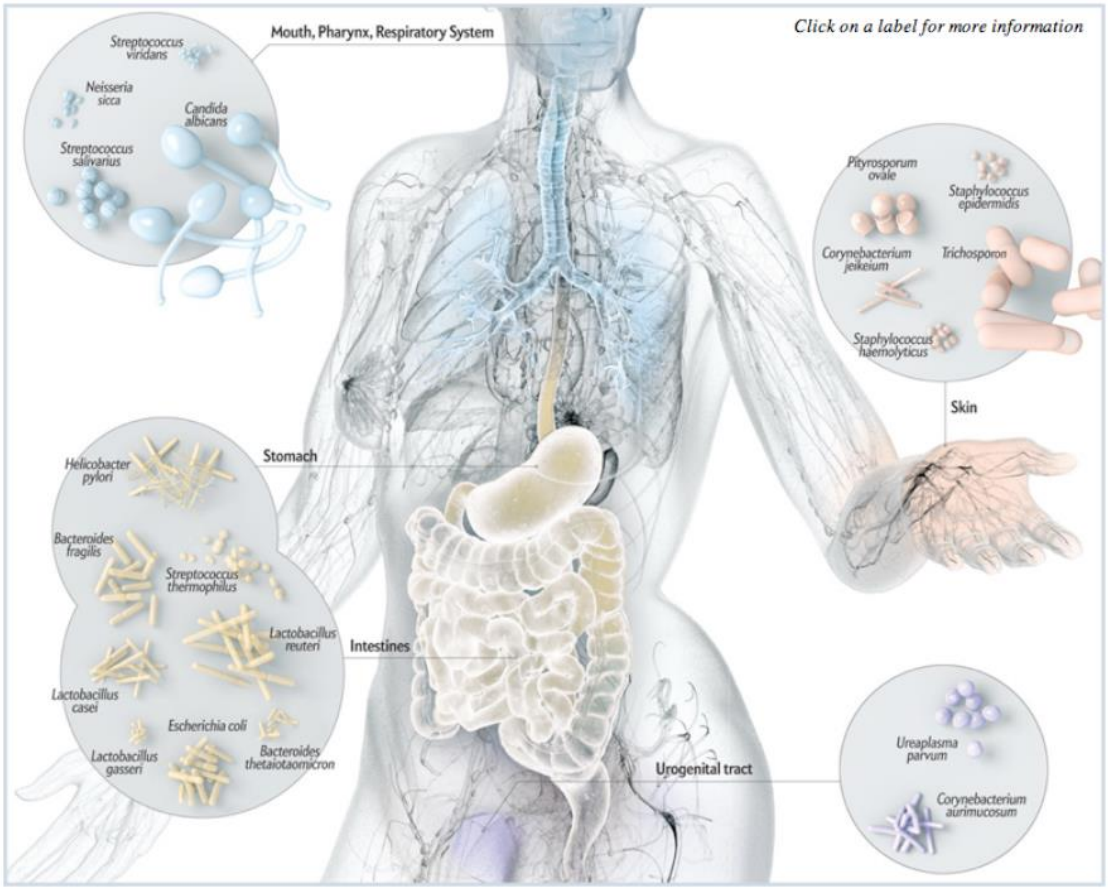
Disclosure

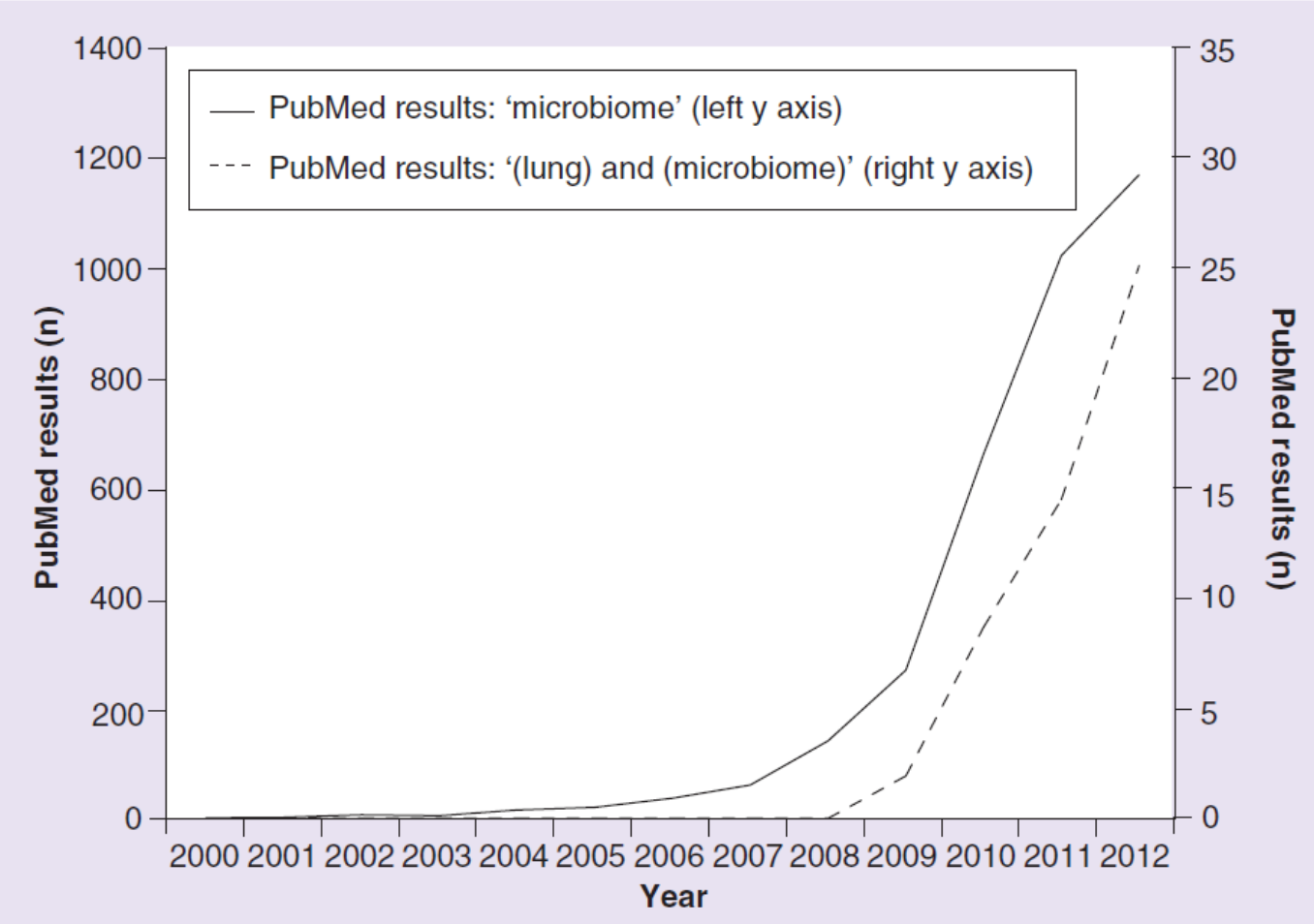
내용

Microbiome and Microbiota

- human microbiome is the collection of all the microorganisms living in association with the human body

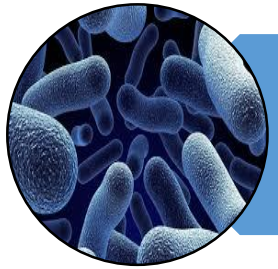


Microbiome: Publication

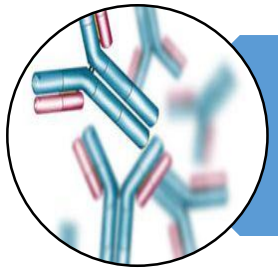


Dickson RP, Expert Rev Respir Med 2013; 7:245-57

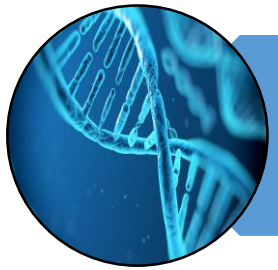
Microbiome: Proof of Presence so far



traditional culture (cultivation)

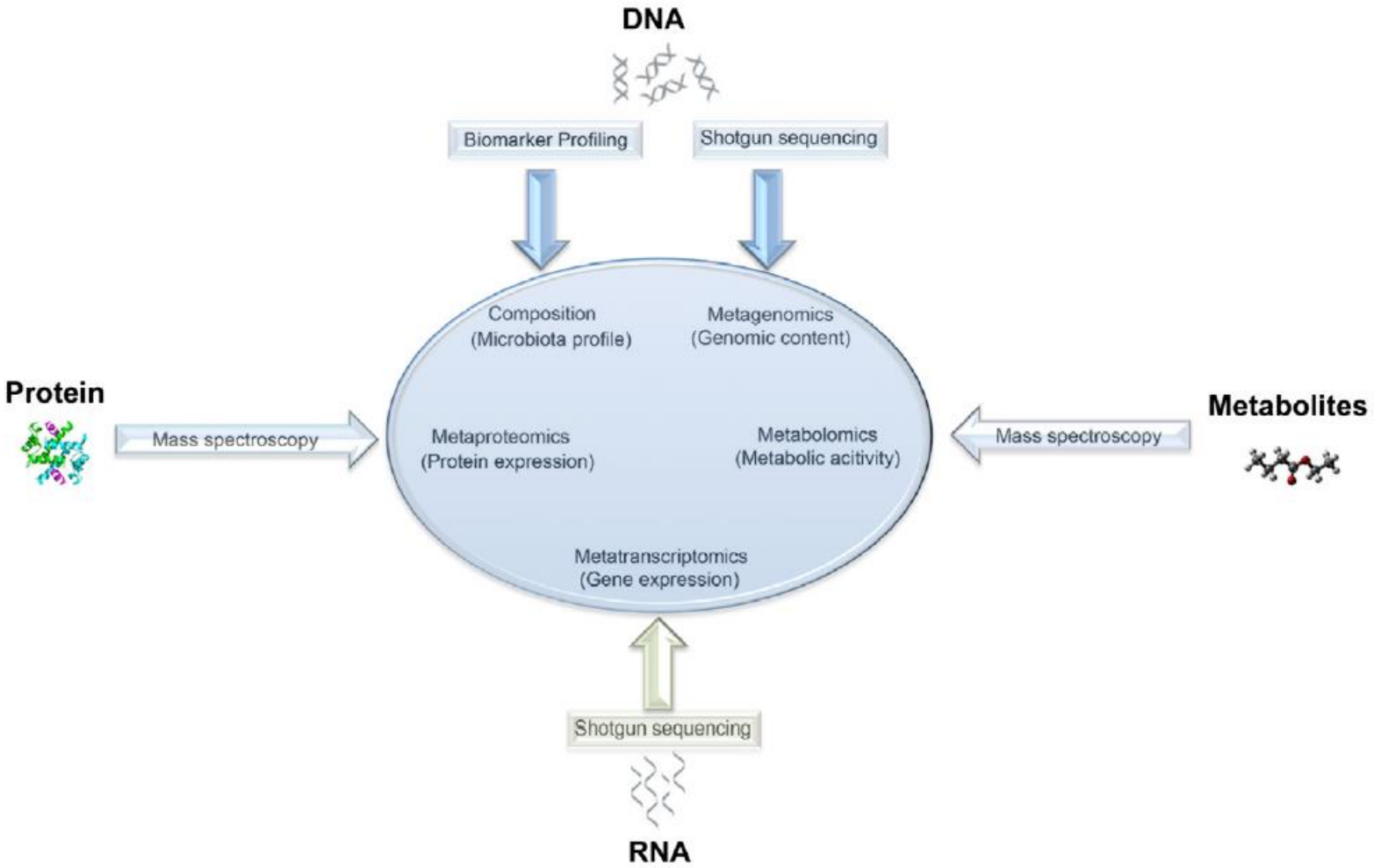


specific serological test



species-targeted PCR

Microbiome: Molecular Tools



Fujimura KE, Lynch SV, Cell Host Microbe 2015; 17:592-602

Metagenome and Metagenomics

- **Metagenome**

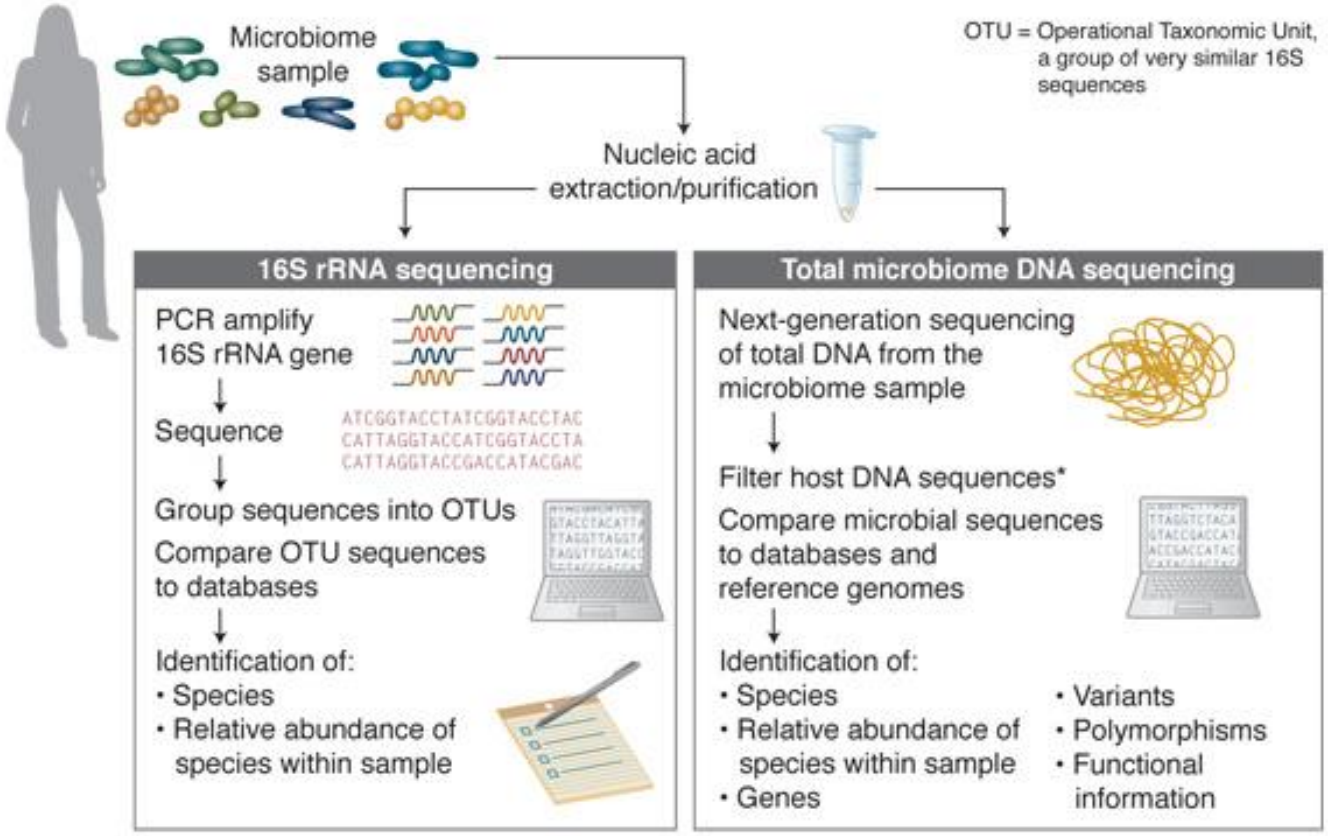
  genetic material recovered directly from environmental samples

  (Wikipedia)

- **Metagenomics**

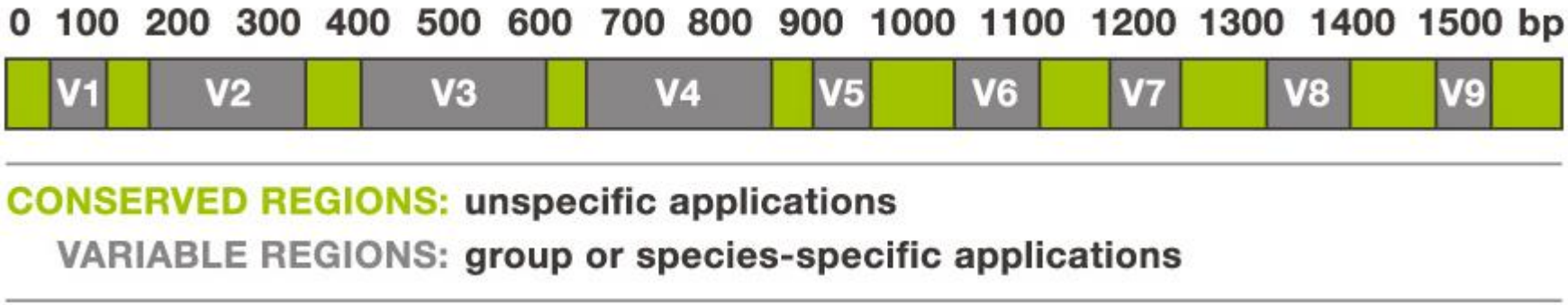
  the study of metagenome

Marker Gene vs. Total (Shotgun) Analysis



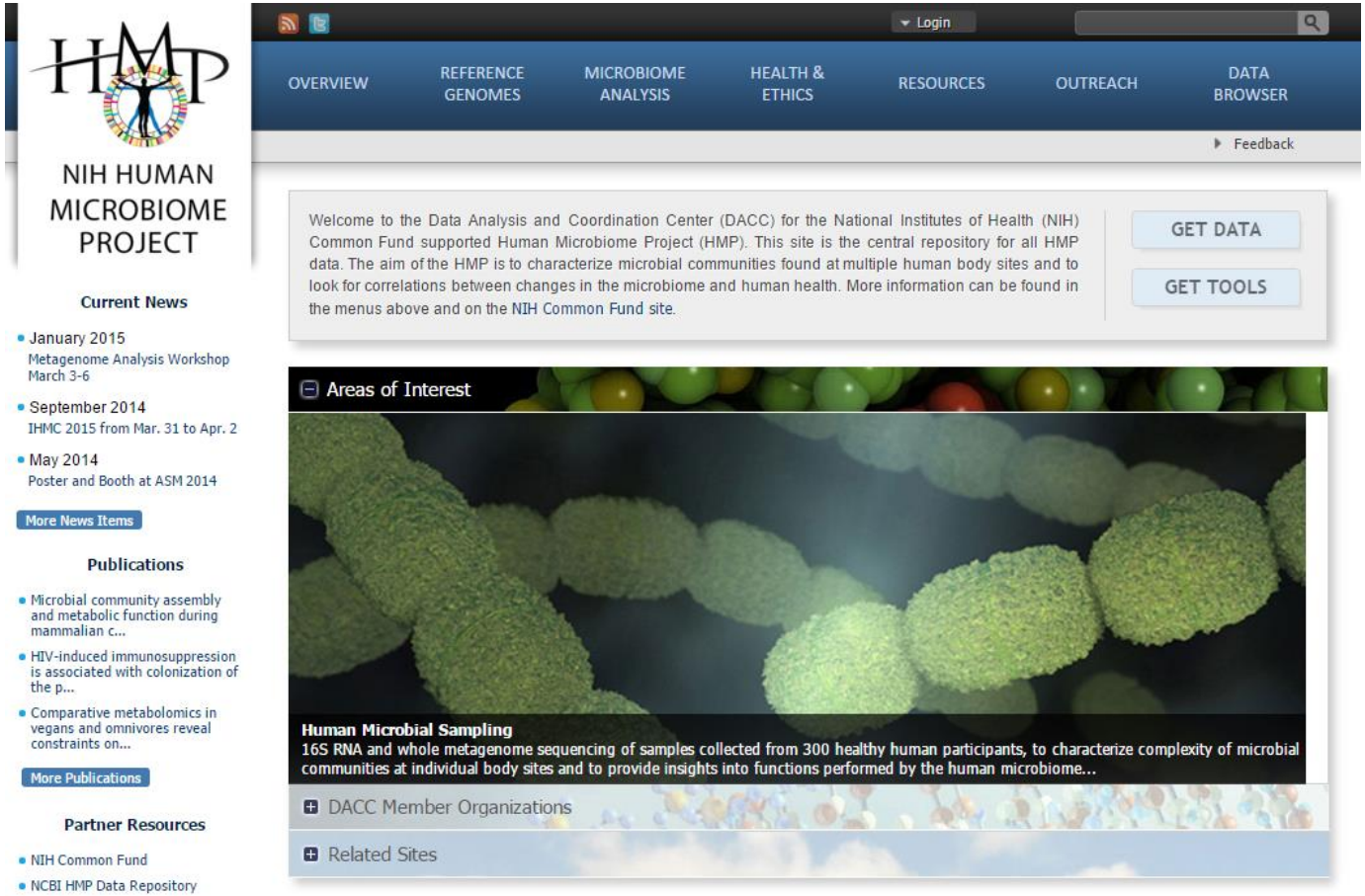
16S ribosomal RNA

- Universal gene (1500 bp)
- Conserved and 9 variable regions
- Comparison of similarity for classification
- Operational Taxonomic Units (OTU) clustering and taxonomic profiling



Human Microbiome Project: 2008-2013

- 300 healthy individuals, across several different sites on the body
  : nasal, oral cavity, skin, GI tract, and urogenital tract

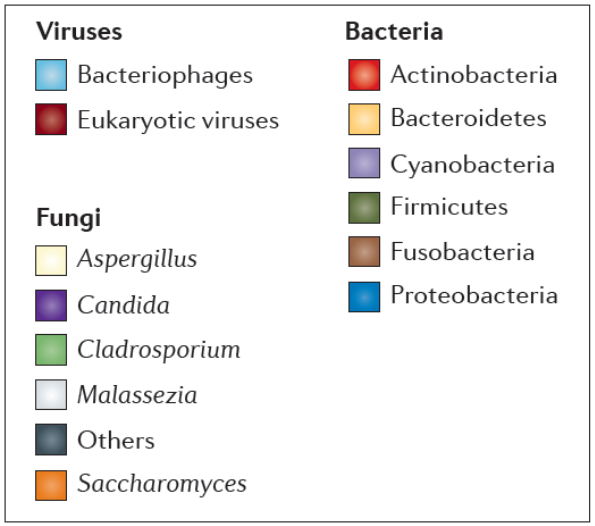


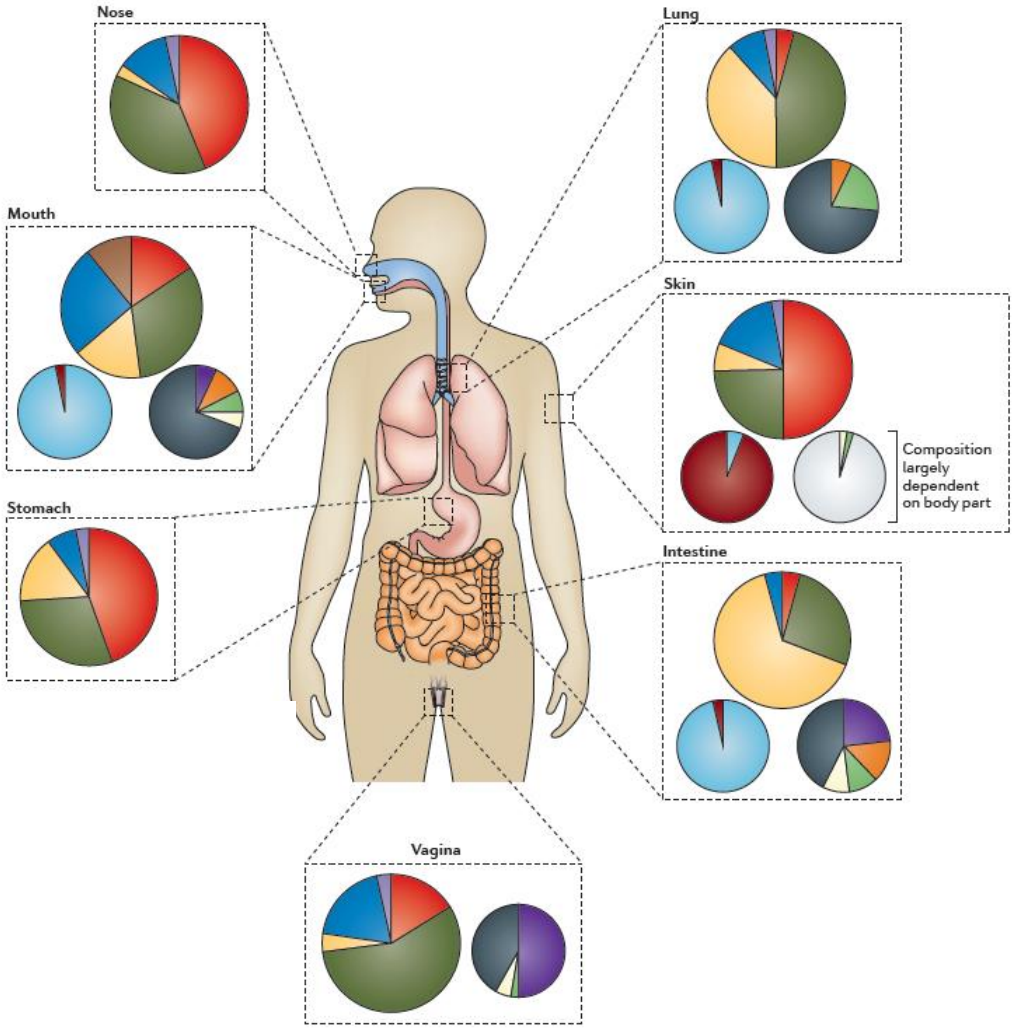
HMP Stage 2: from 2014-

correlations between changes in the microbiome and health

- Project 1: Pregnancy & Preterm Birth
- Project 2: Inflammatory Bowel Disease
- Project 3: Prediabetes

Microbiome Composition: Habitat dependent





Marsland BJ, Gollwitzer ES. Nat Rev Immunol 2014; 14:827-35

Microbiome: Roles

- They do Nothing? or Something good or bad?
- Gut microbiome is involved in
  - absorption of nutrients
  - synthesis of vitamins
  - metabolism of xenobiotics
  - Immune modulation
- Site specific roles

Lung Microbiome

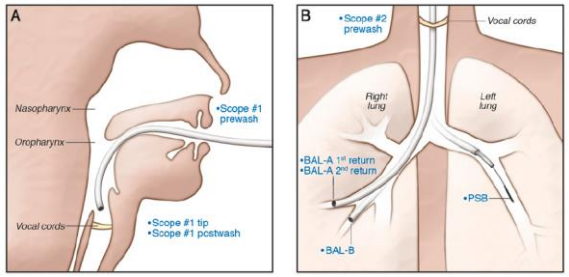
- What is there?
- What is the physiological role?
- Association with diseases? Then how?

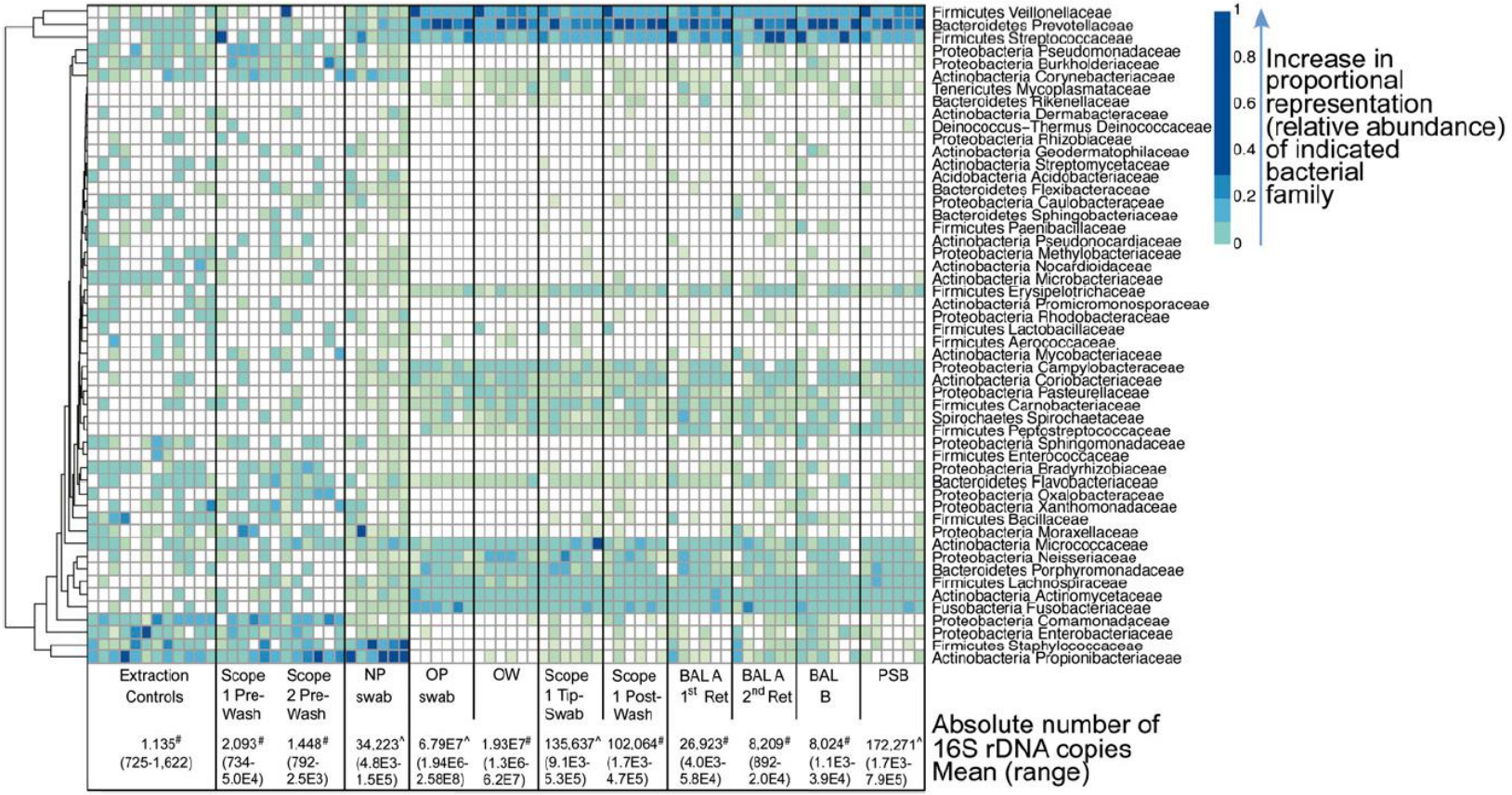


Lung Microbiome: versus Gut

- Lower biomass
- Less diverse
- Risk of contamination from the upper airway during sampling

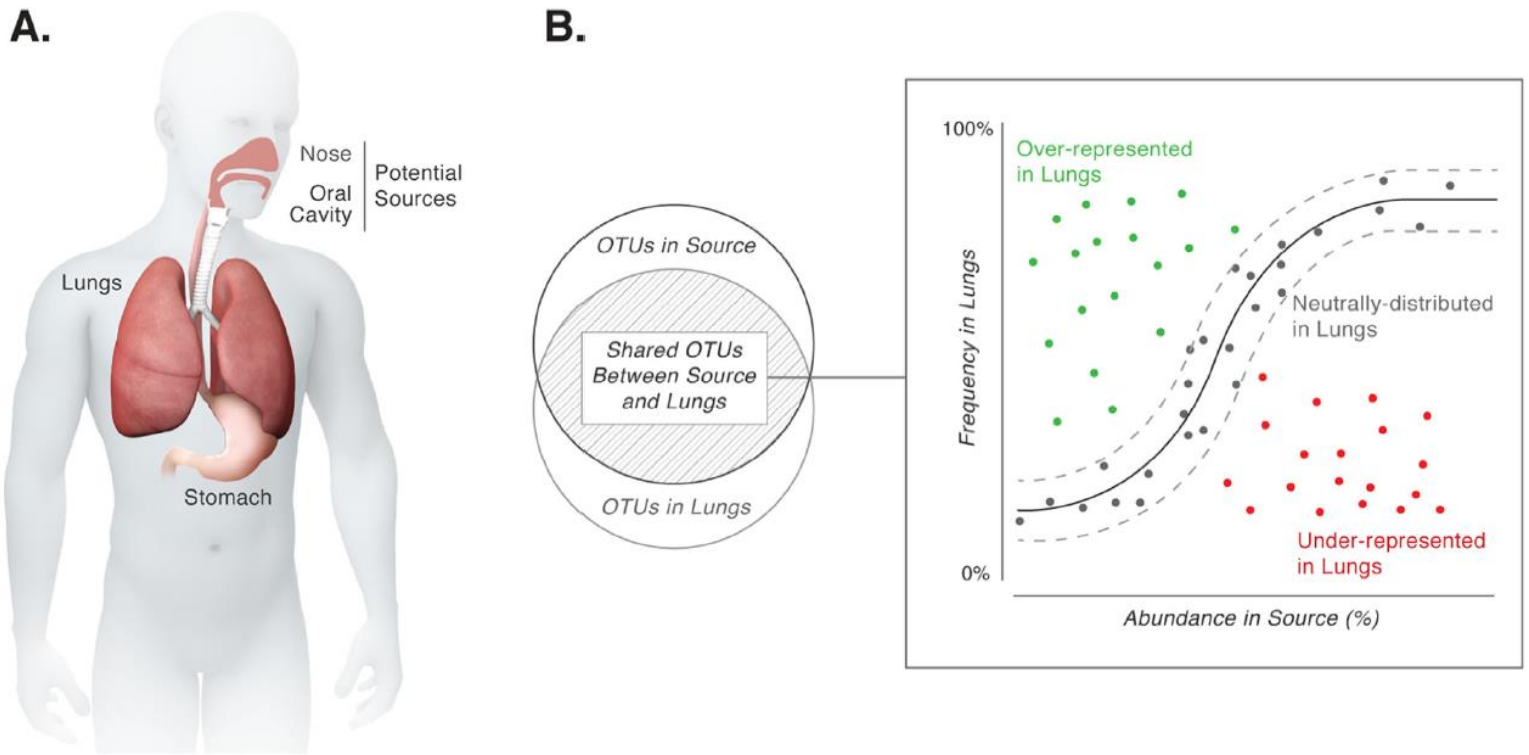
Lung Microbiome: in healthy subjects





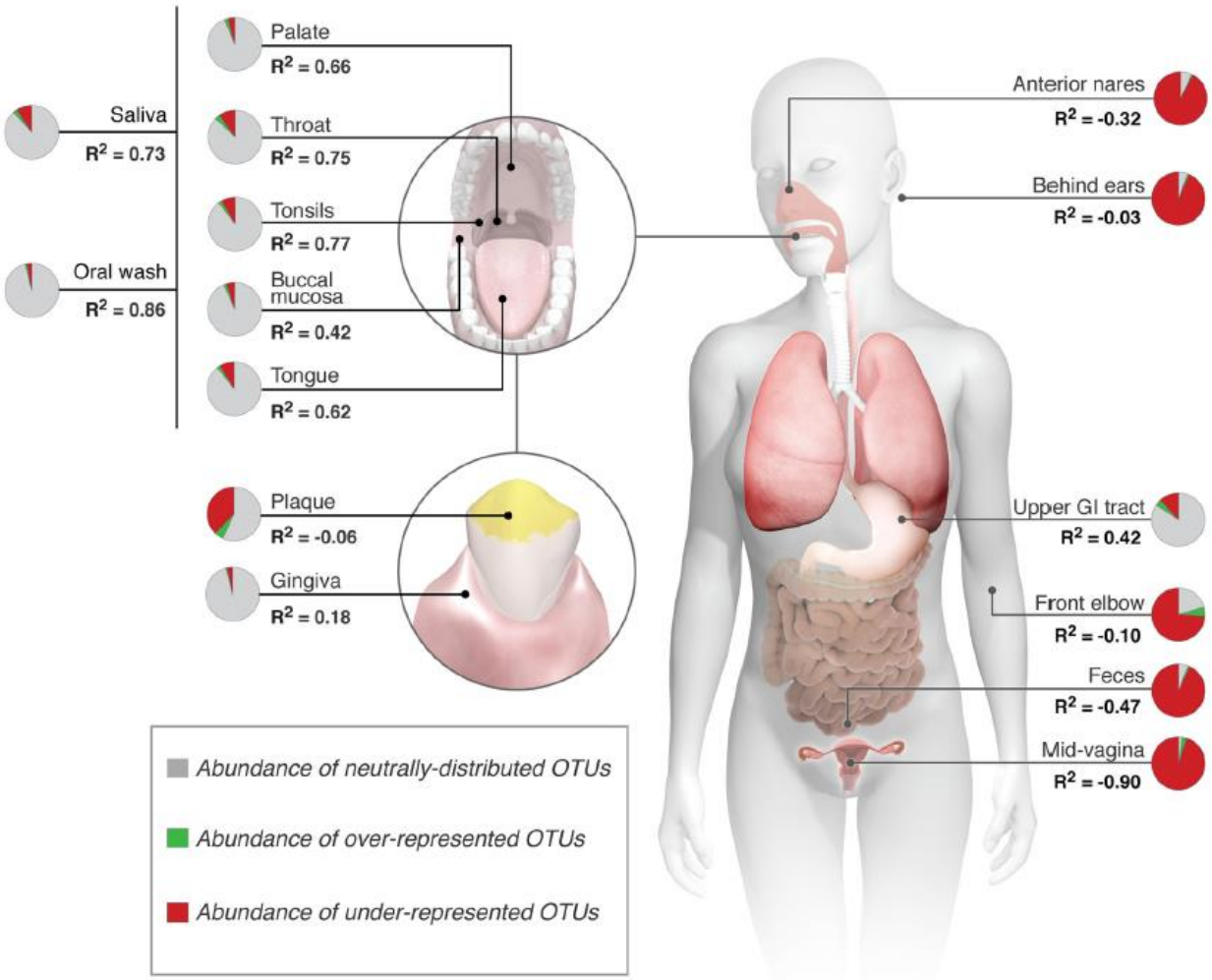
Charlson ES et al., Am J Respir Crit Care Med 2011; 184:957-63

Lung Microbiome: Possible Origin



Venkataraman A et al., MBio 2015; 6

Lung Microbiome: Possible Origin



Venkataraman A et al., MBio 2015; 6

Lung Microbiome: In healthy subjects

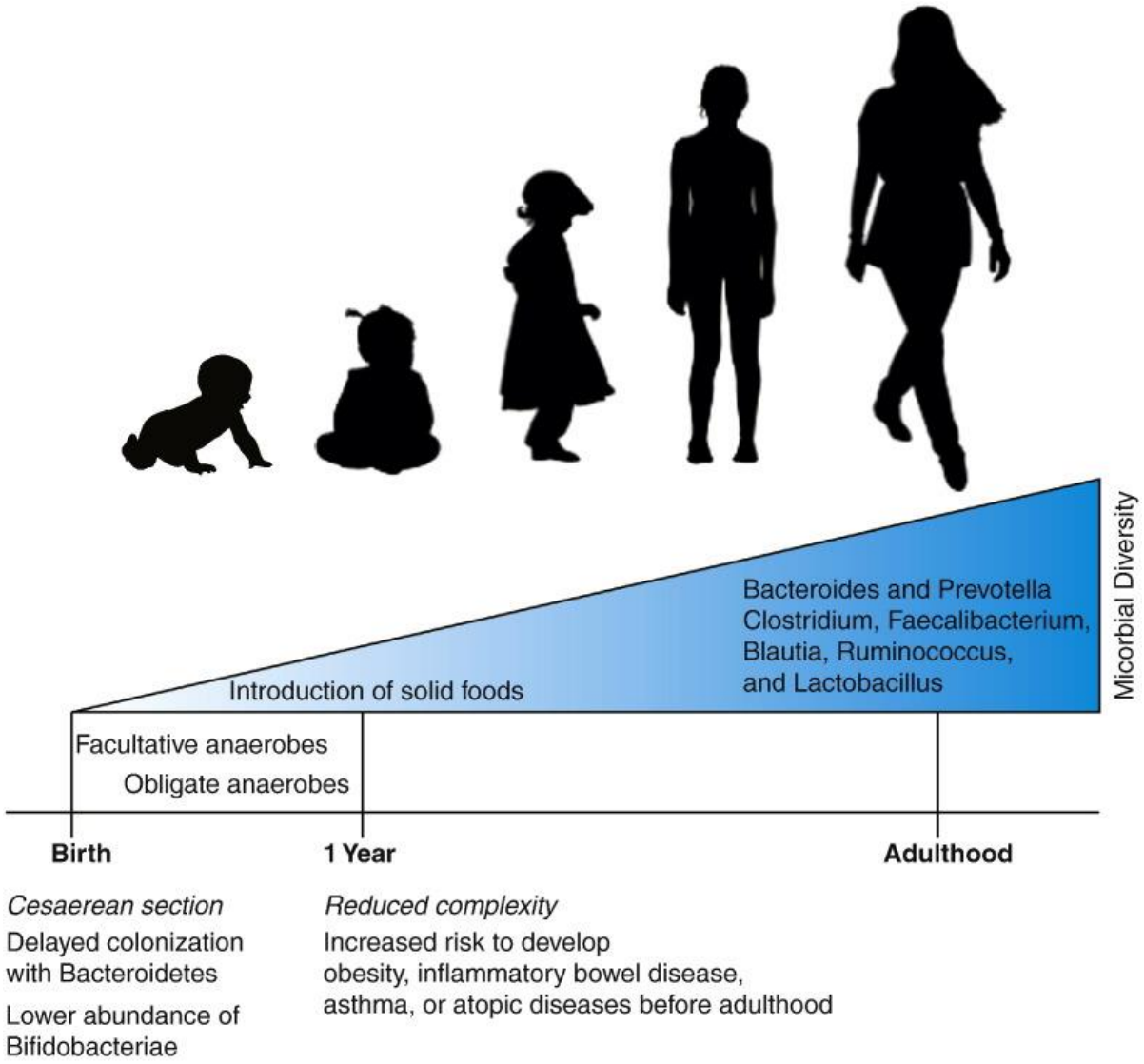
- Phylum level by abundance

Phylum (문)	Bacteroidetes	Firmicutes	Proteobacteria
Genus (속)	• Prevotella • Bacteroides	• Veillonella • Streptococcus • Staphylococcus	• Pseudomonas • Haemophilus • Moraxella • Neisseria • Acinetobacter • Escherichia

Microbiome: possible affecting factors

- Age
- Ethnicity
- Diet
- Smoking
- Mode of birth (delivery)
- Antibiotics and probiotics

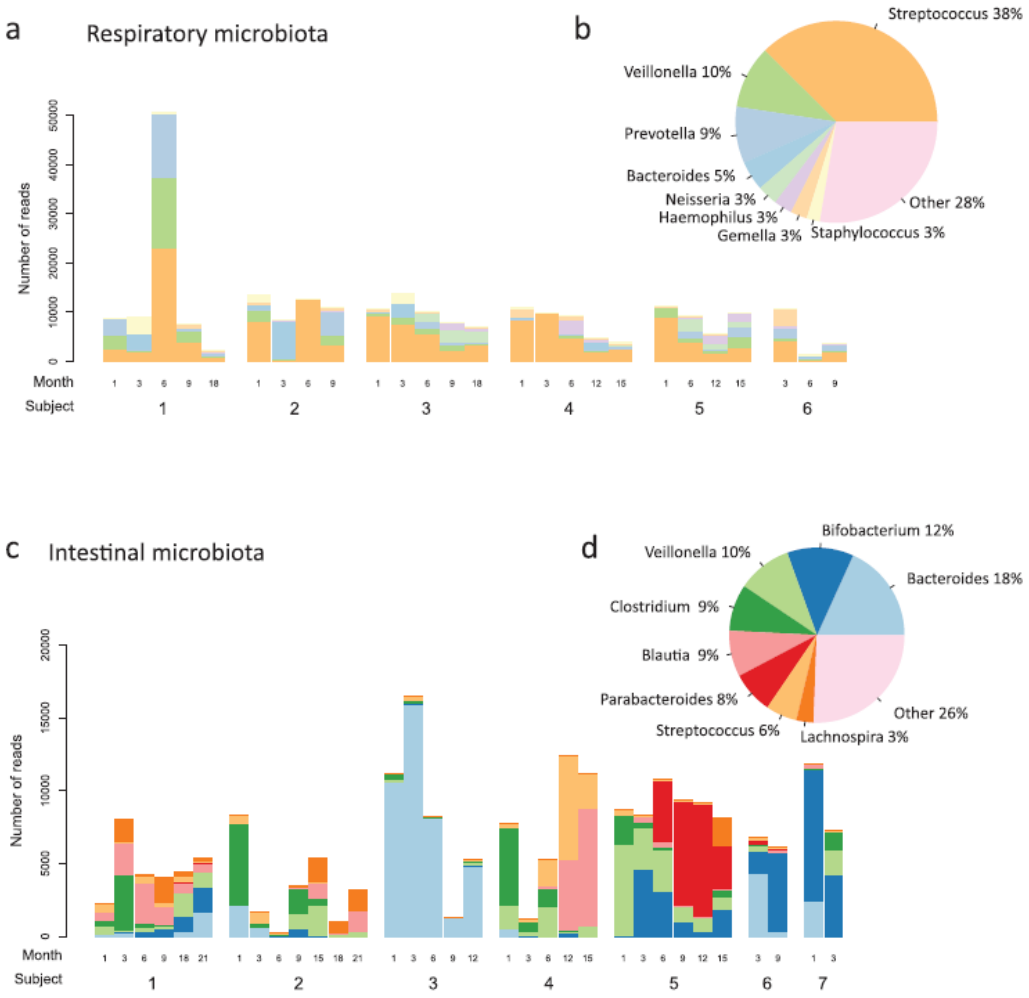
Gut Microbiome: Changes & Diversity



McCoy KD, Koller Y, Clin Immunol 2015; 159:170-6

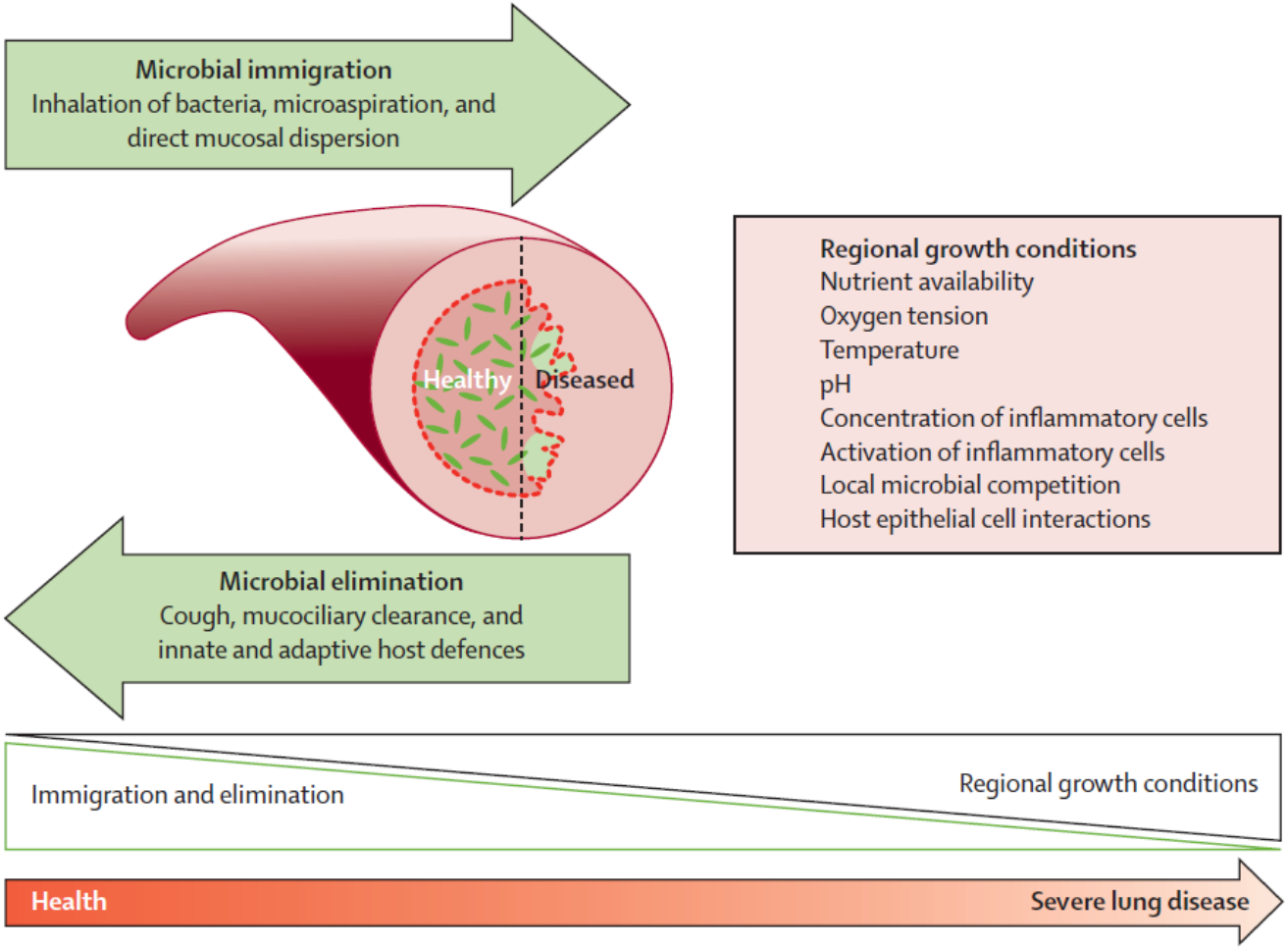
Microbiome: Stability over Time

- Serial Analysis of the Gut and Respiratory Microbiome in Cystic Fibrosis in Infancy



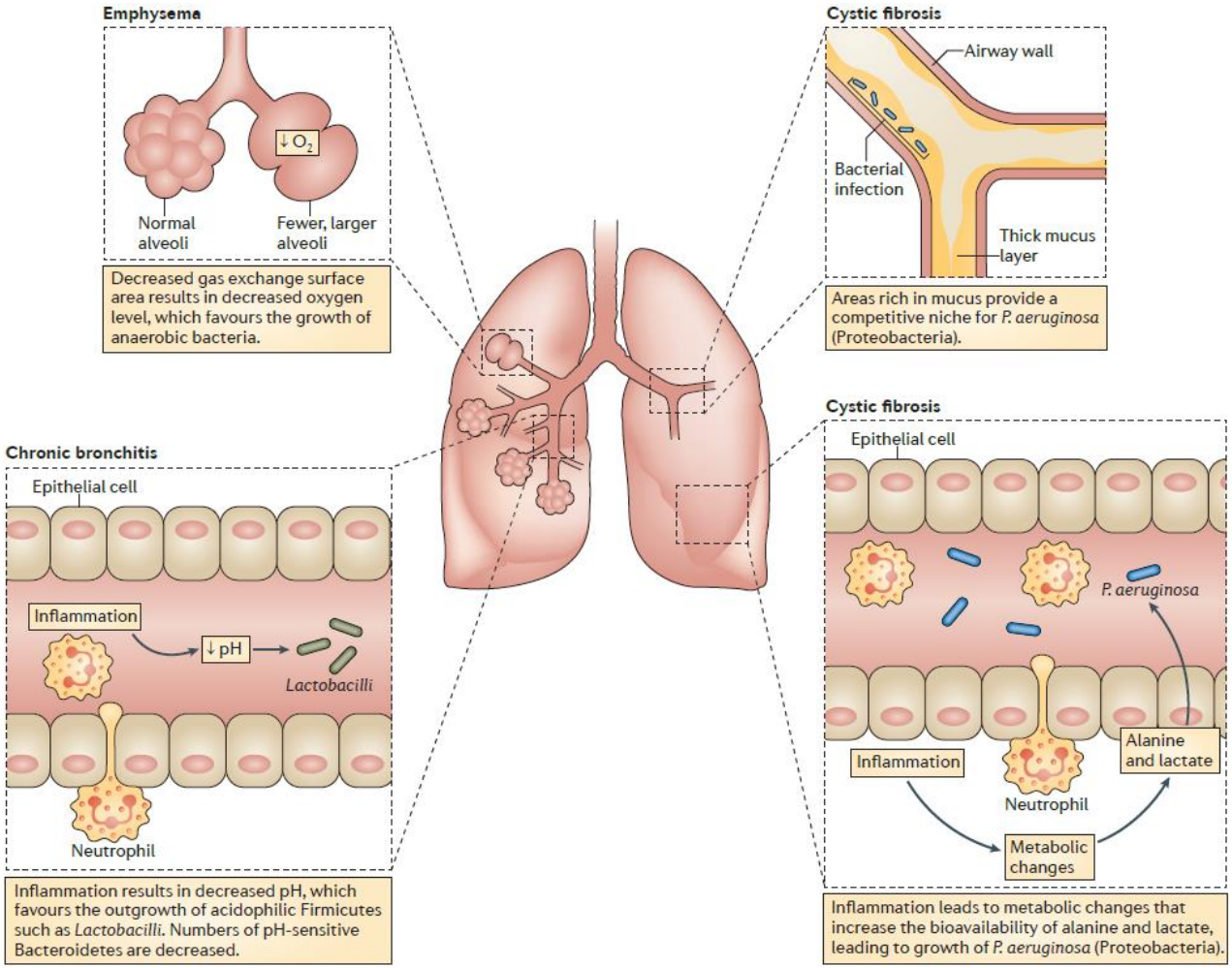
Madan JC et al., MBio 2012; 3

Lung Microbiome: 3 Major Determinants



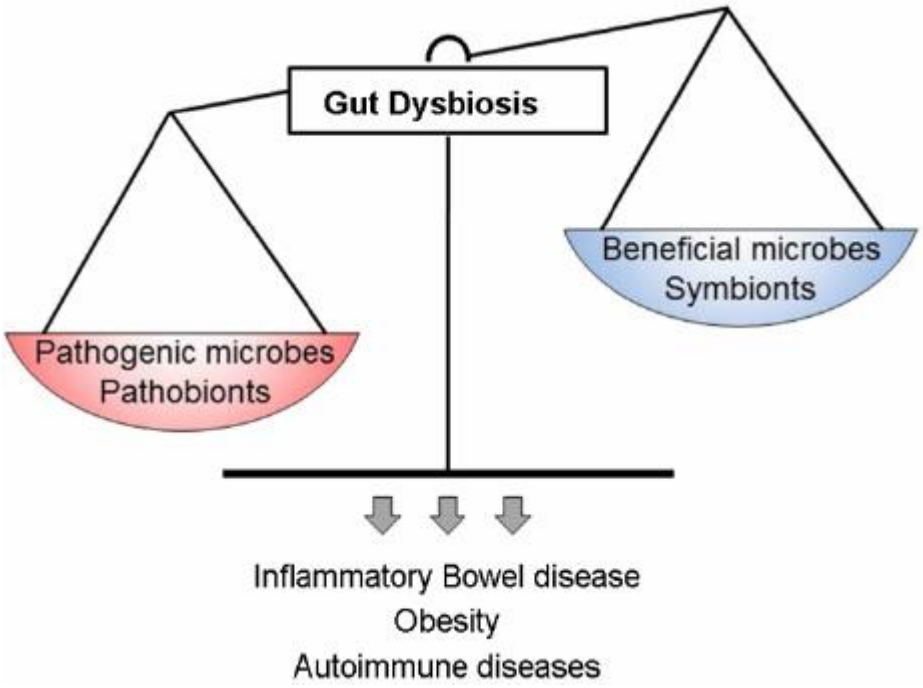
Dickson RP et al., Lancet 2014; 384:691-702

Lung Microbiome: affected by local sites



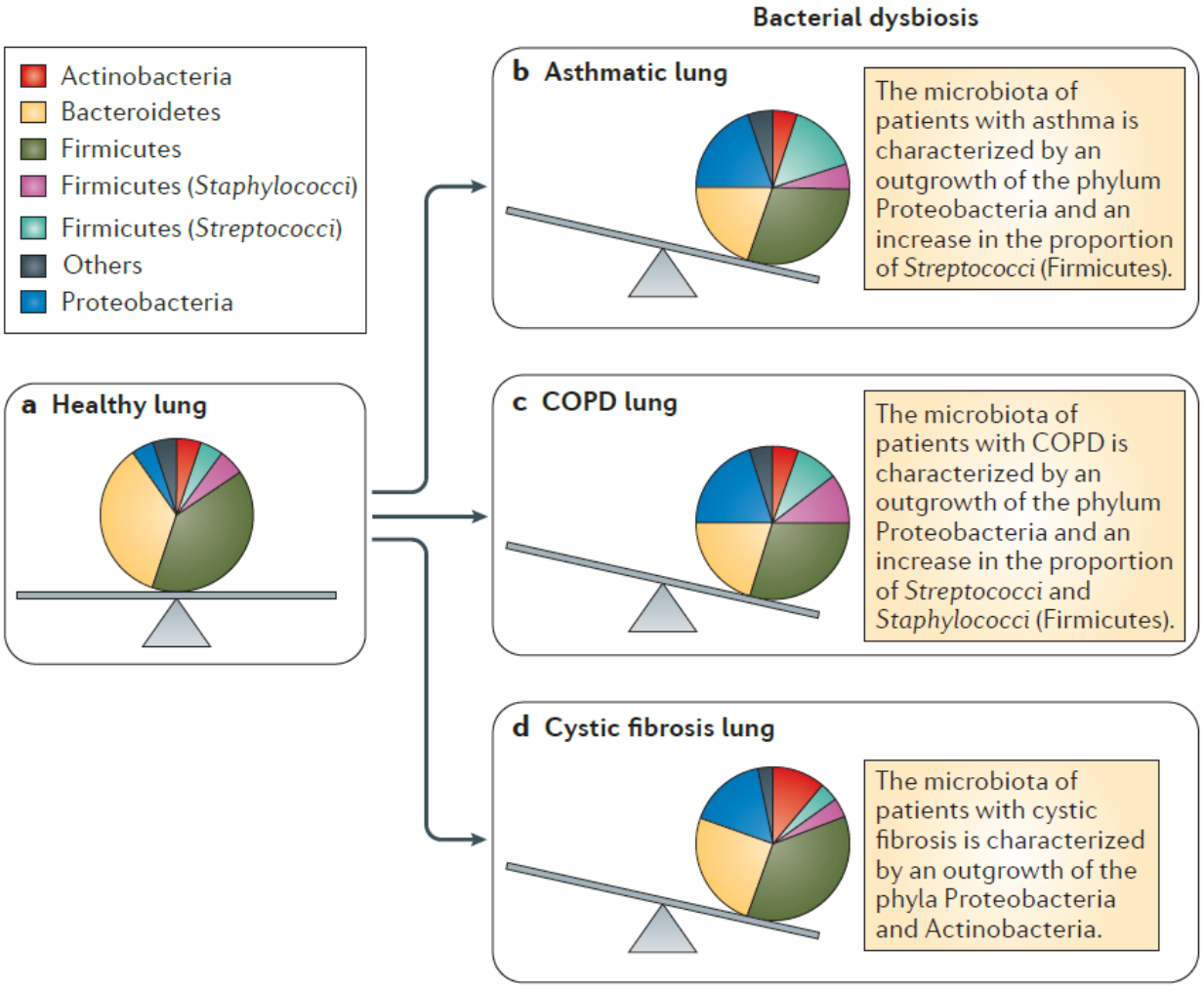
Marsland BJ, Gollwitzer ES. Nat Rev Immunol 2014; 14:827-35

Gut Dysbiosis and Diseases



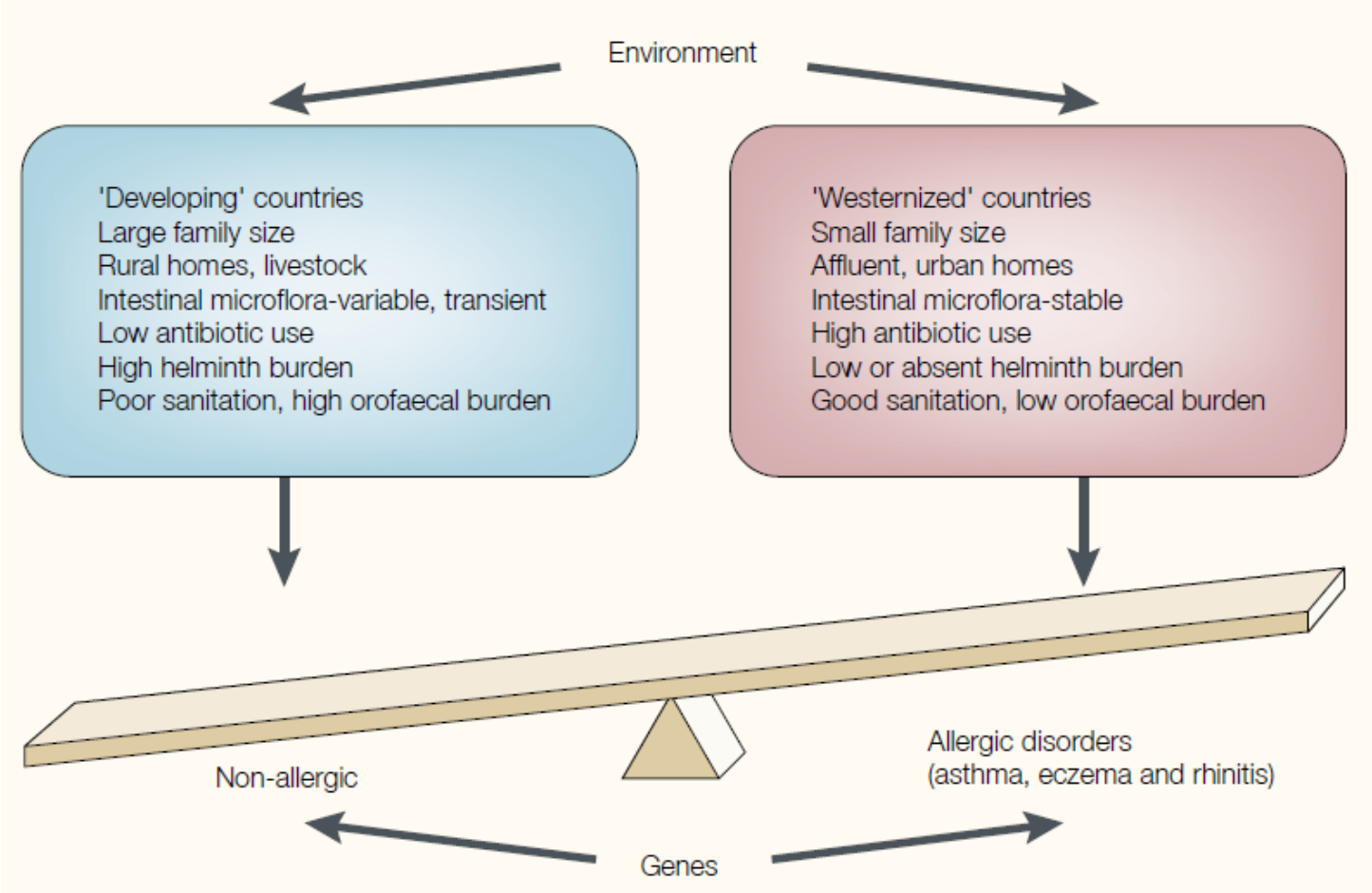
Mazmanian SK, Lee YK, J Bacteriol Virol 2014; 44:1-9

Lung Microbiome: dysbiosis and diseases



Marsland BJ, Gollwitzer ES. Nat Rev Immunol 2014; 14:827-35

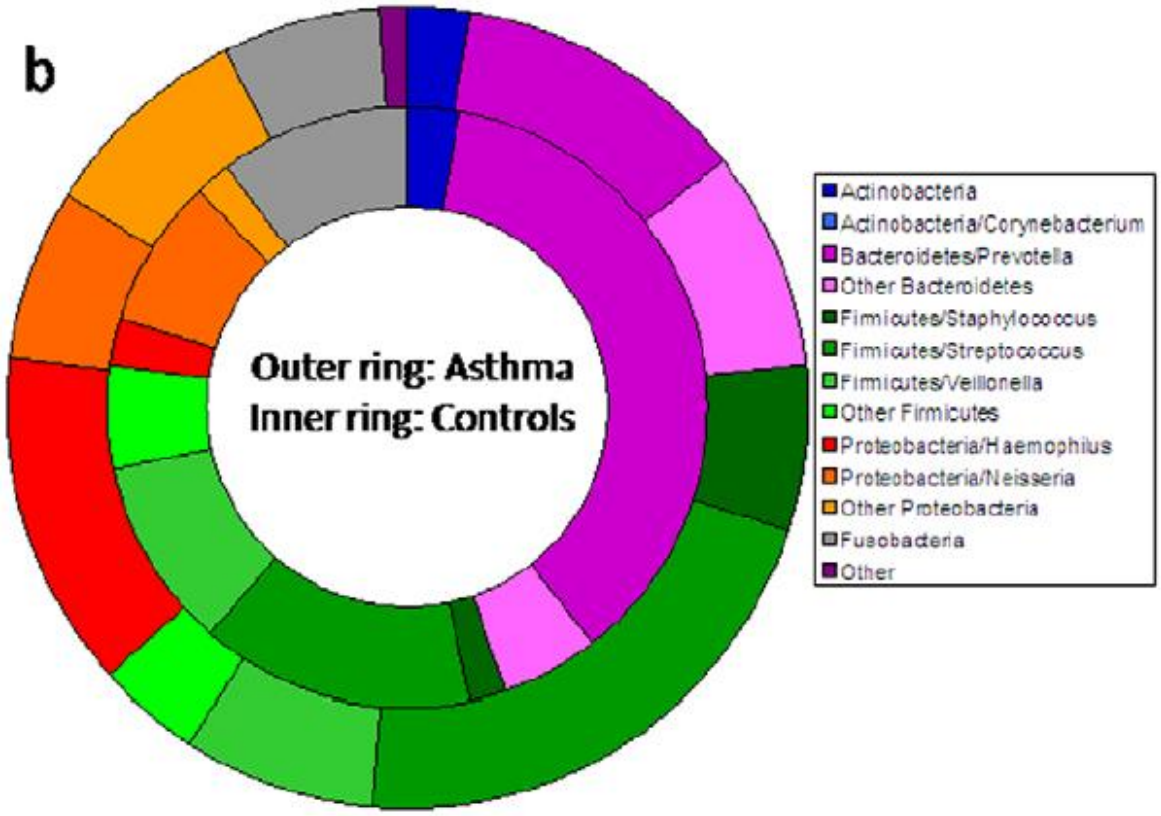
Microbiome may explain Hygiene Hypothesis



Wills-Karp M et al., Nat Rev Immunol 2001; 1:69-75

Asthma Microbiome: BAL from Children

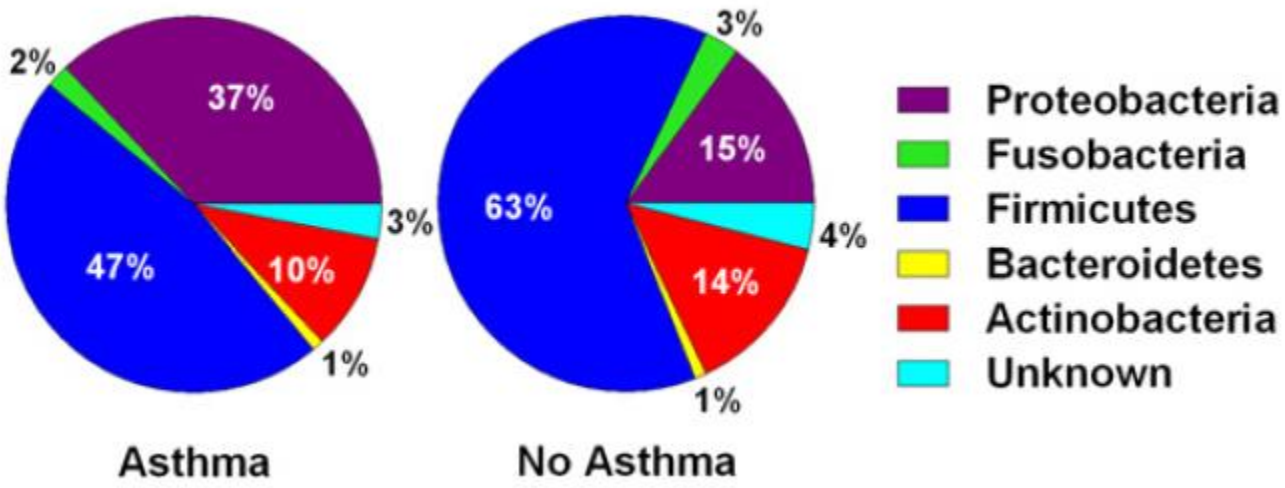
- broncho-alveolar lavage (BAL) in children with difficult asthma and controls
- Proteobacteria, particularly *Haemophilus* spp., were much more frequent.



Hilty M et al., PLoS One 2010; 5:e8578

Asthma Microbiome: Sputum from adults

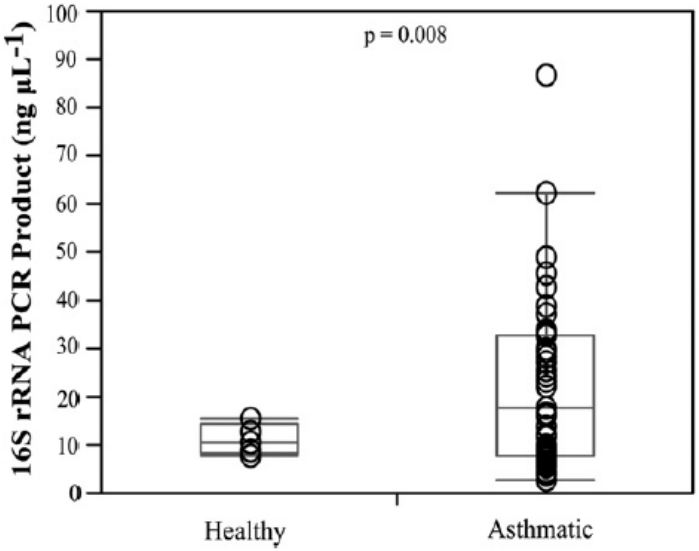
- Induced sputum from 10 adults with mild asthma (8/10, no ICS use) and 10 controls
- Confirmation of greater prevalence of Proteobacteria

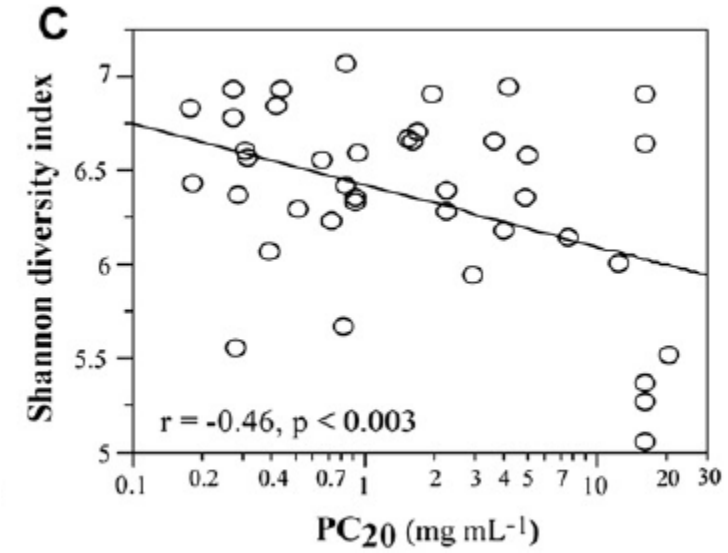


Marri PR et al., J Allergy Clin Immunol 2013; 131:346-52 e1-3

Asthma Microbiome: association with AHR

- 16S ribosomal RNA amplicon concentrations (a proxy for bacterial burden) higher in asthma
- bacterial diversity were significantly higher among asthmatic patients.

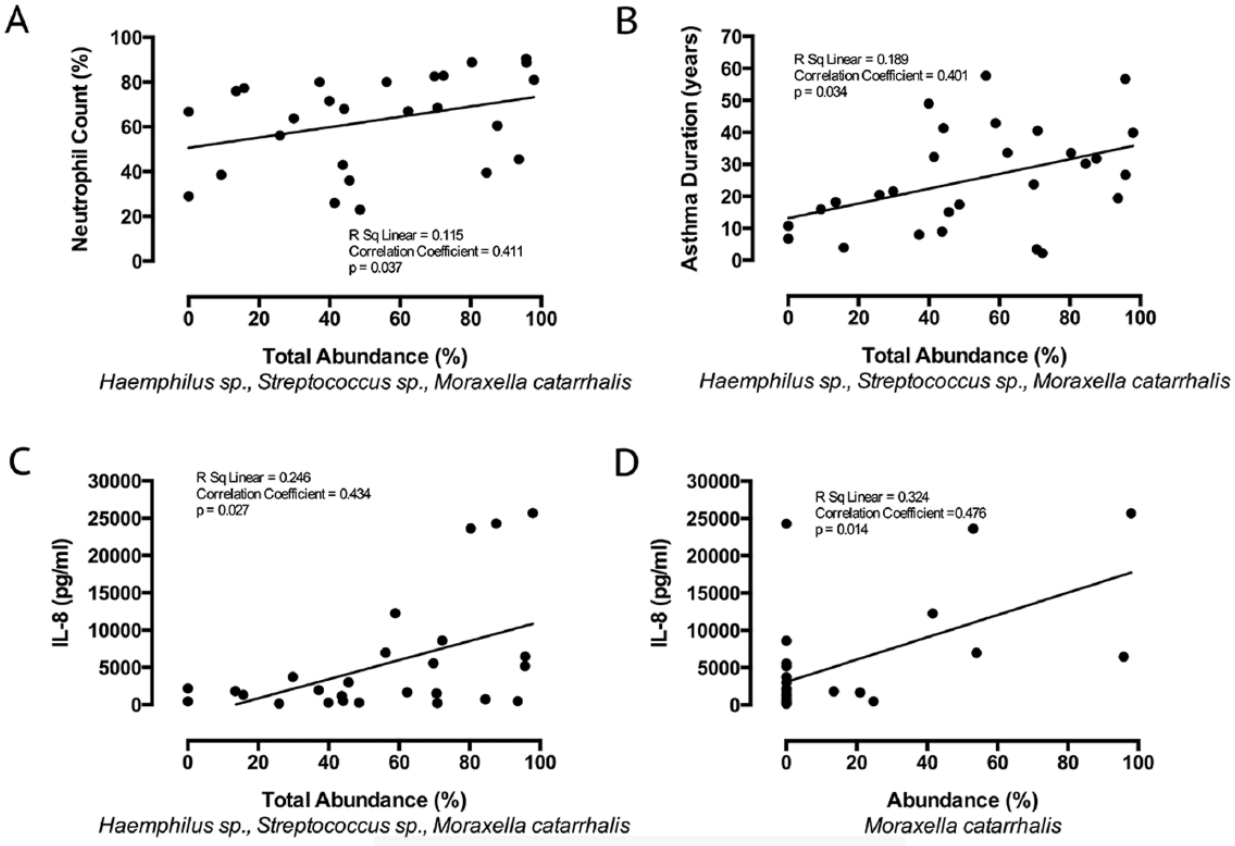




Huang YJ et al., J Allergy Clin Immunol 2011; 127:372-81 e1-3

Asthma Microbiome: association with phenotypes

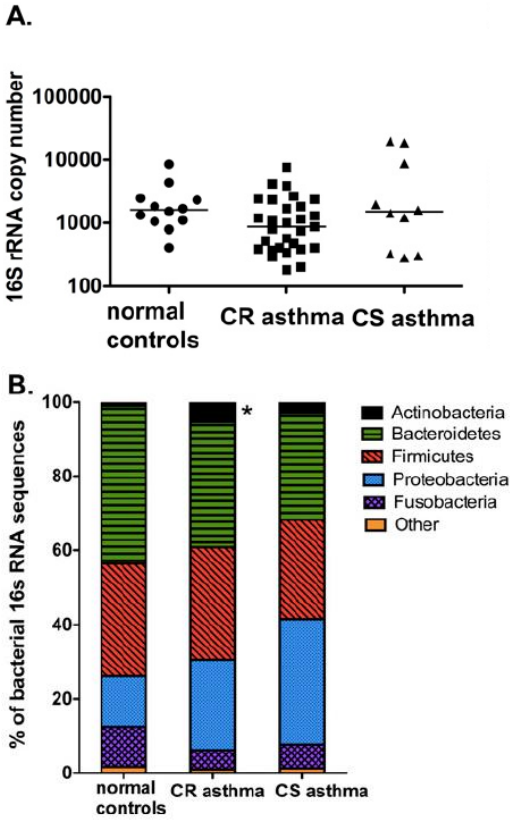
- Sputum from 28 adult patients with treatment-resistant asthma
- relative abundance of *M. catarrhalis, Haemophilus* or *Streptococcus* correlated with longer asthma duration, worse lung function and higher sputum neutrophil counts and IL-8 concentrations.

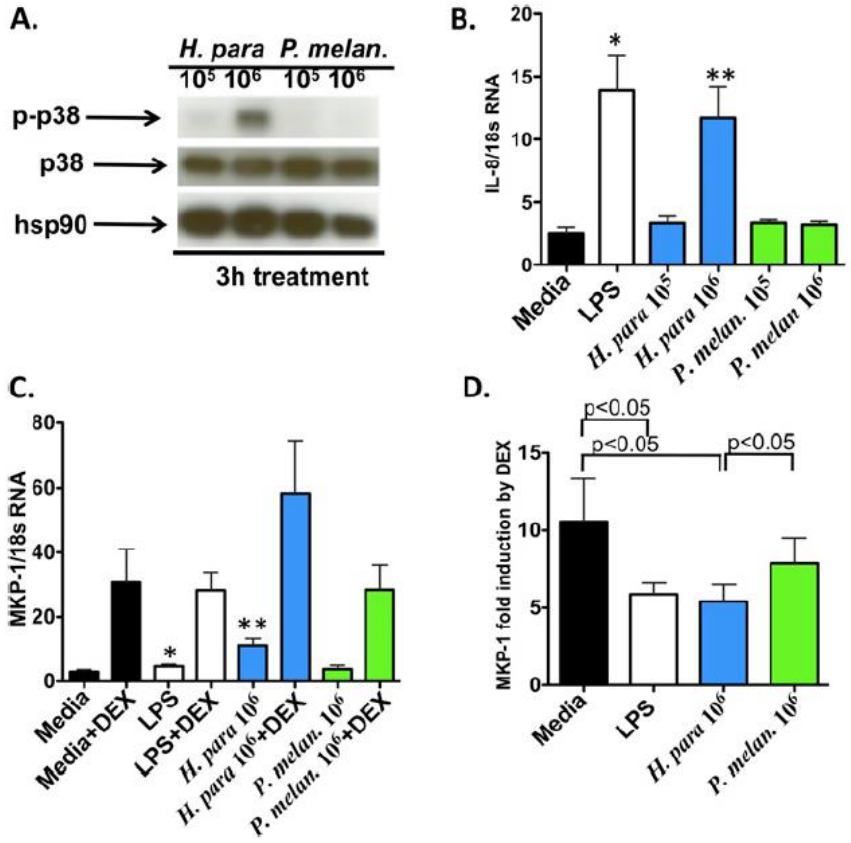


Green BJ et al., PLoS One 2014; 9:e100645

Asthma Microbiome
: association with oral steroid response

- BAL from 39 asthmatics and 12 controls
- No significant response in phylum level between CR and CS, while subset of patients with CR have an increased prevalence of *Haemophilus parainfluenzae*
- PBMC culture with *H. parainfluenzae* led to their activation and resistance to corticosteroid inhibition

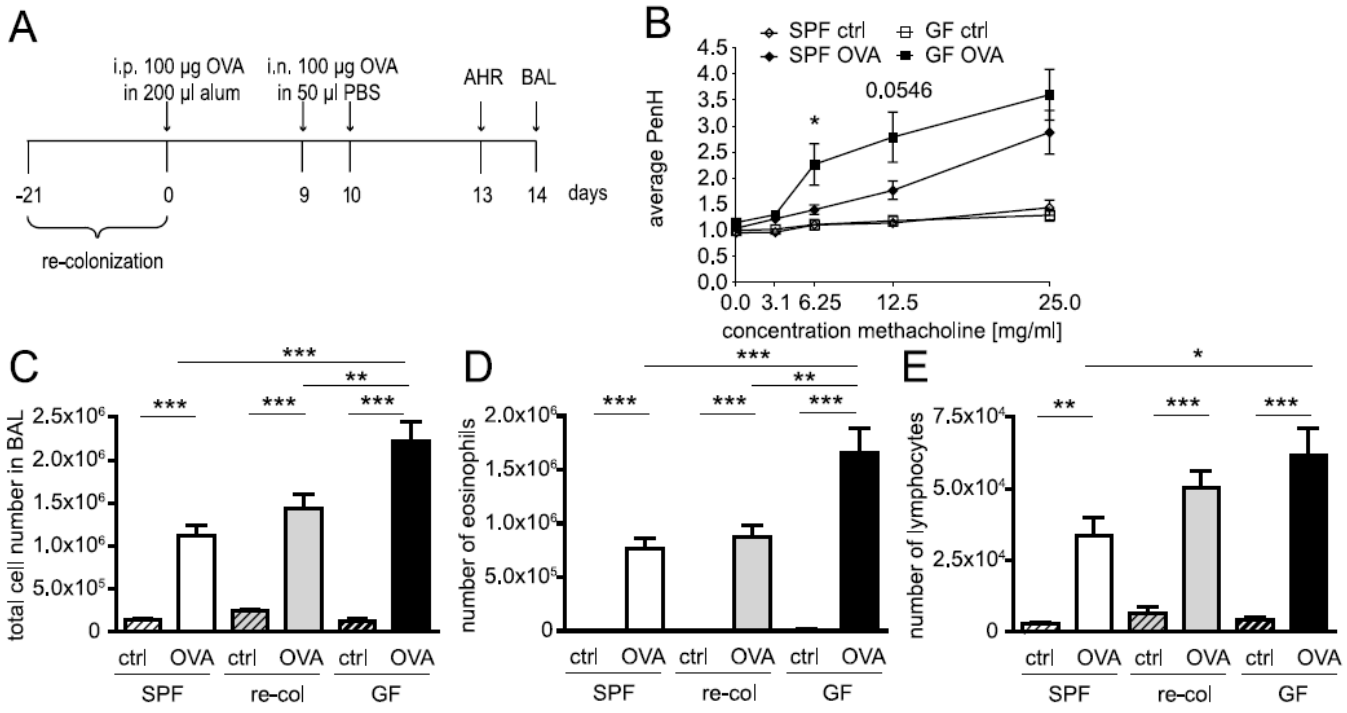




Goleva E et al., Am J Respir Crit Care Med 2013; 188:1193-201

Mice Experiments
: Allergic Airway Inflammation influenced by Microbial Colonization

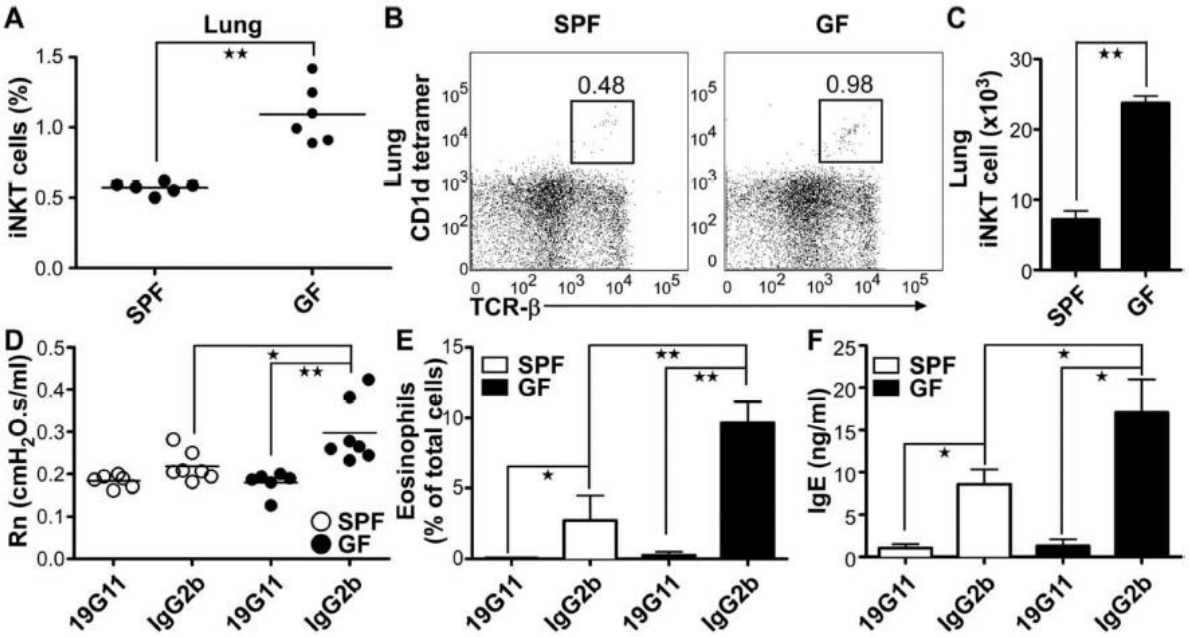
- lack of microbial colonization (Germ Free, GF) leads to increased allergic airway inflammation
- recolonization before allergen exposure is able to rescue the phenotype



Herbst T et al., Am J Respir Crit Care Med 2011; 184:198-205

Mice Experiments
: microbial exposure in early life has effects on iNKT cell function

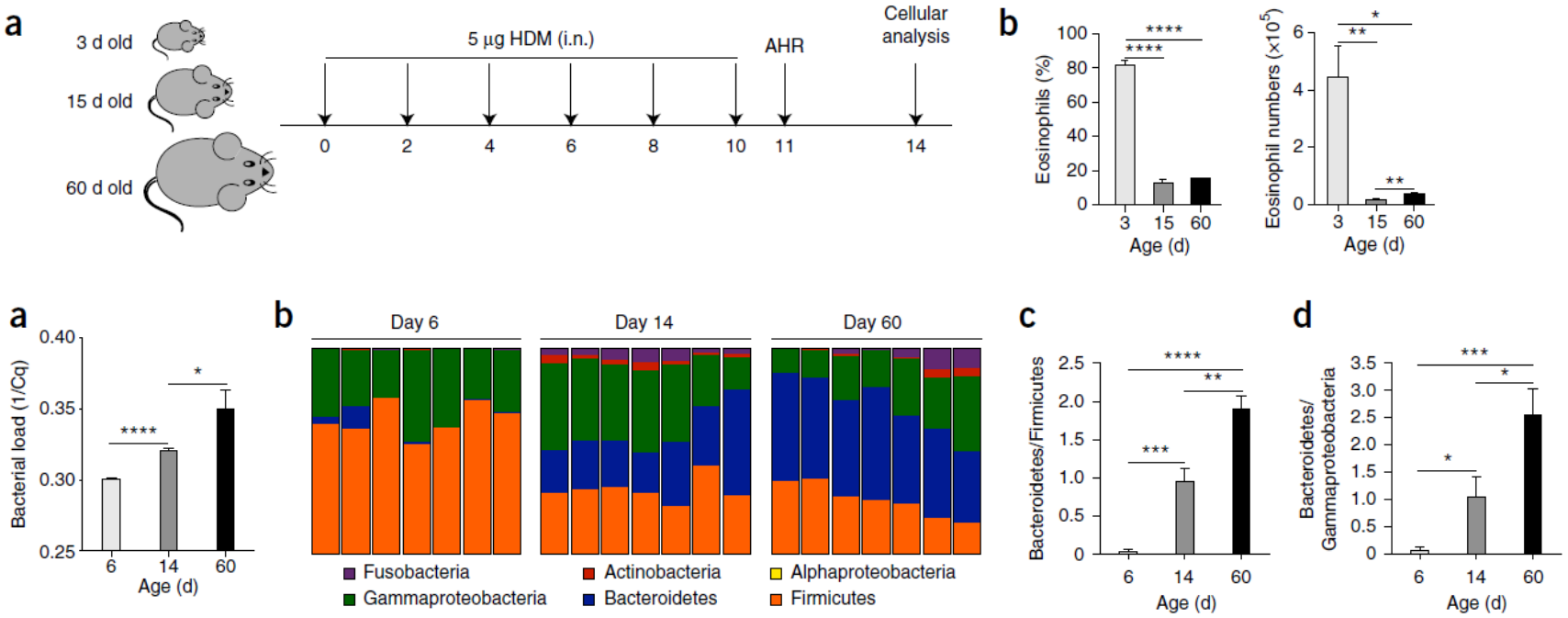
- Germ-free mice, which have exaggerated allergic responses, maintain a population of iNKT cells in the lungs that perpetuate the allergic responses.
- iNKT cell bias was only rectified if the mice were recolonized with a normal microbiota within the first 10 days after birth



Olszak T et al., Science 2012; 336:489-93

Mice Experiments
: Lung microbiota promotes tolerance to allergens in neonate via PD-L1

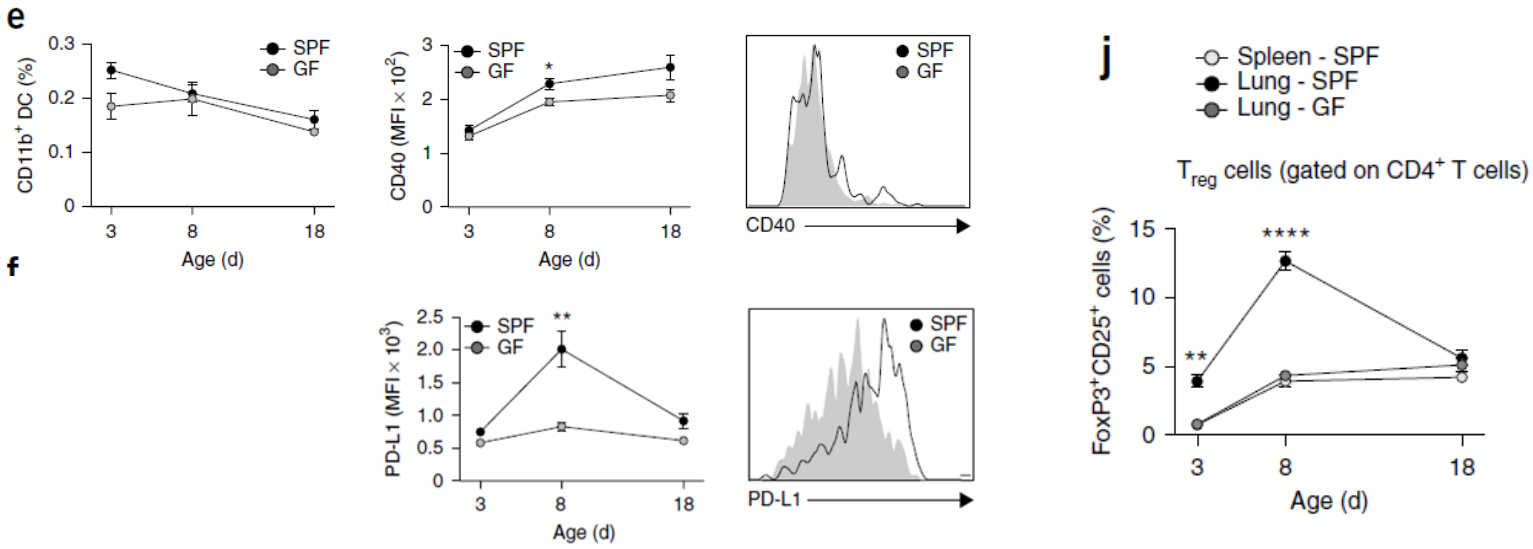
- development-related changes in lung bacterial load and community composition were associated with decreased airway responses to aeroallergen exposure



Gollwitzer ES et al., Nat Med 2014; 20:642-7

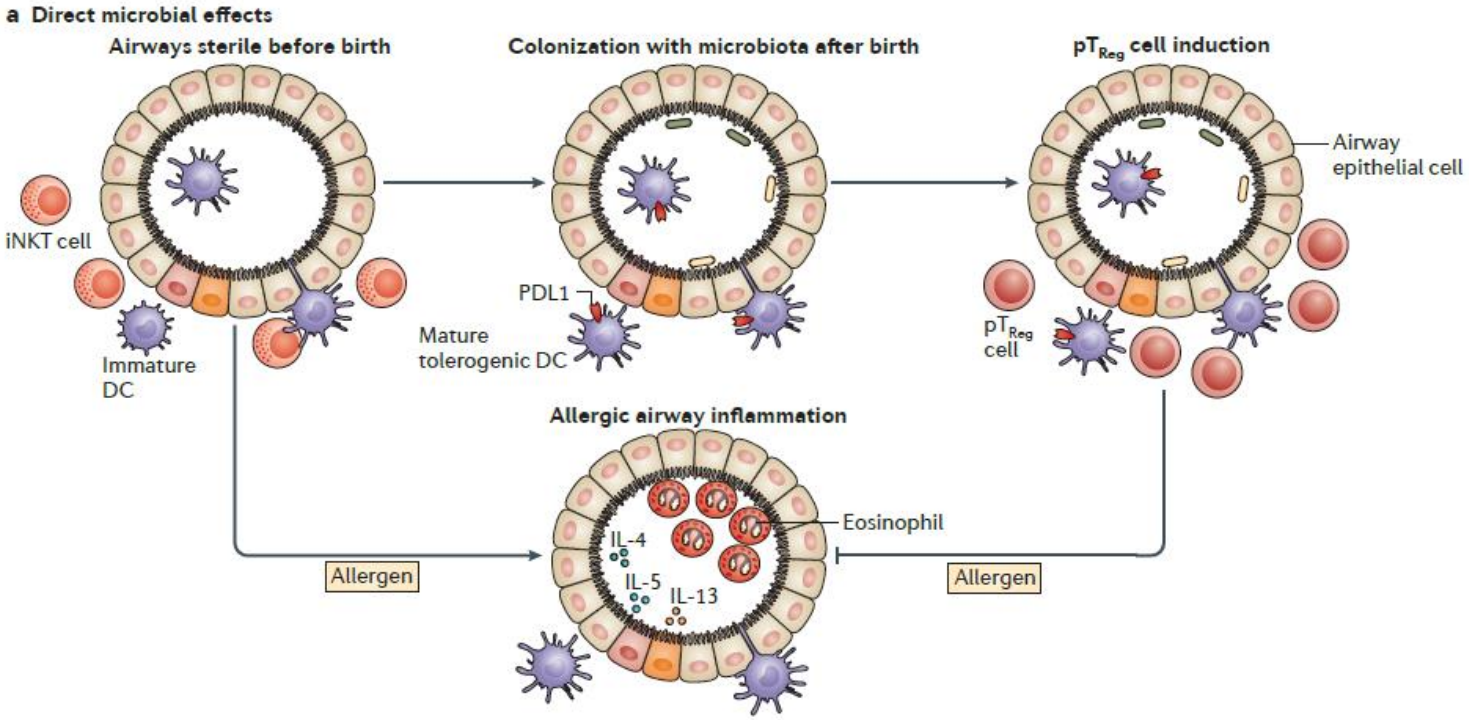
Mice Experiments
: Lung microbiota promotes tolerance to allergens in neonate via PD-L1

- tolerance was not associated with the existing presence of high numbers of regulatory T (Treg) cells in the lung at birth
- Tolerance induction with the development of a different Treg cell subset that seemed to require microbial presence during a critical early window after birth.



Gollwitzer ES et al., Nat Med 2014; 20:642-7

Lung Microbiome: Immune Modulating Effects

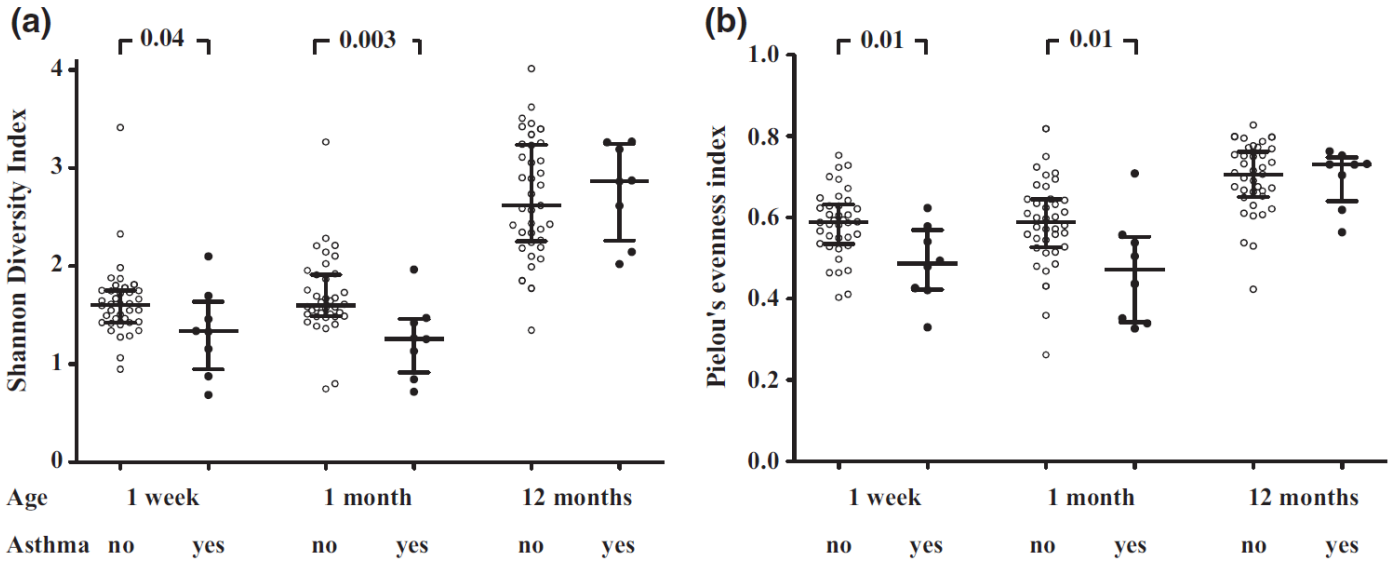


Marsland BJ, Gollwitzer ES. Nat Rev Immunol 2014; 14:827-35

Gut Microbiome offers clues to Asthma

Asthma: decreased gut microbiome diversity

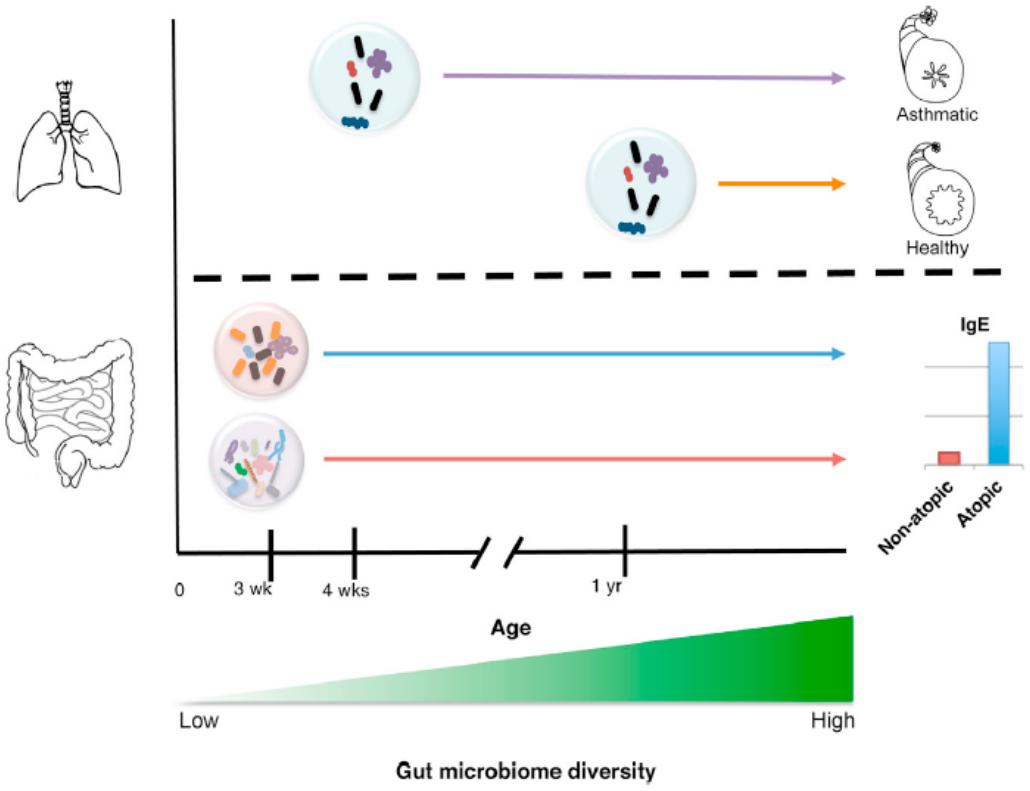
- children with asthma (at 7 years of age) have a lower intestinal bacterial diversity in the first month after birth



Abrahamsson TR et al., Clin Exp Allergy 2014; 44:842-50.

Very-Early-Life Exposures Influence Asthma and Allergy Development

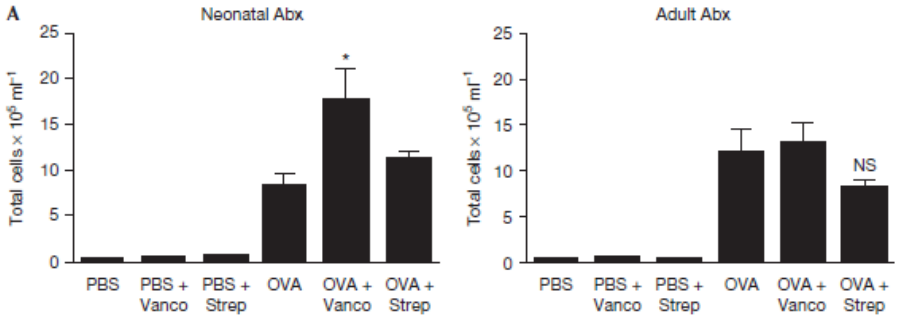
- Intestinal microbial diversity during early-life colonization shapes long-term IgE levels

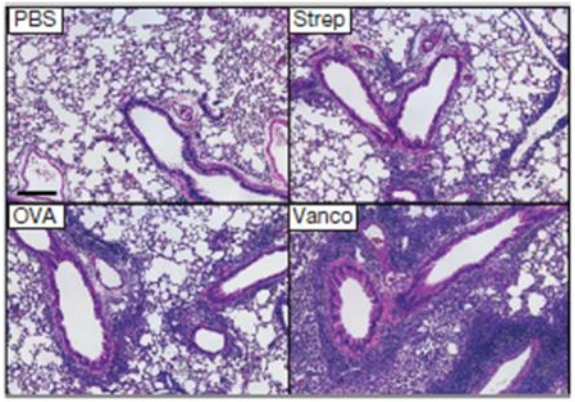


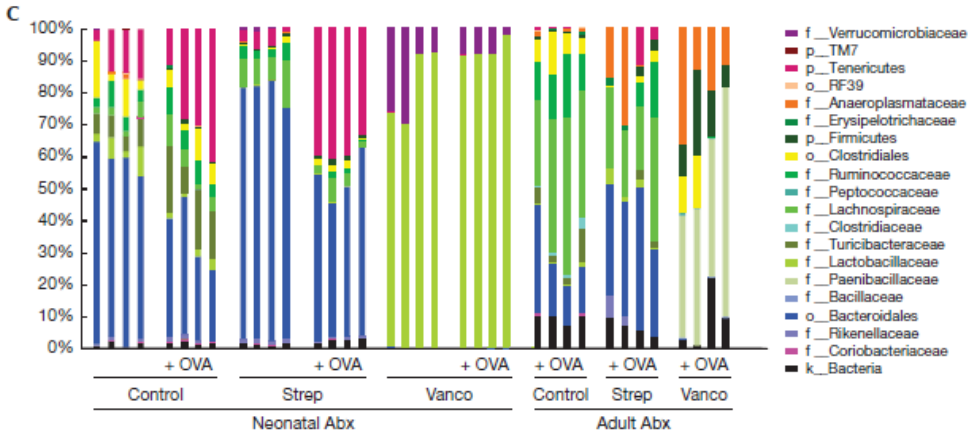
Cahenzli J et al., Cell Host Microbe 2013; 14:559-70
Fujimura KE, Lynch SV, Cell Host Microbe 2015; 17:592-602

Mice Experiments
: Early life antibiotic-driven changes in microbiota affects asthma

- Vancomycin in neonates, not in adults, affected asthma susceptibility
- reduced microbial diversity, shifted the composition of the bacterial population



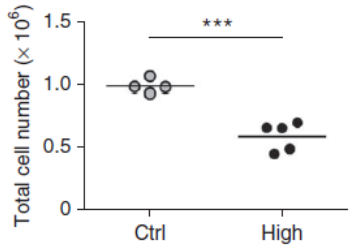


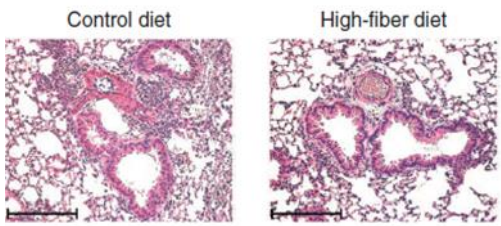


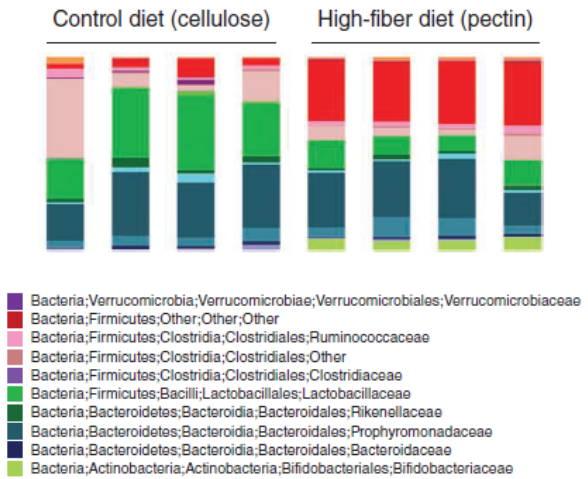
Russell SL et al., EMBO Rep 2012;13:440-7

Diet affects Asthma by changing Gut Microbiome

- Mice with high fiber diet were protected against allergic lung inflammation with gut microbiota change and increased circulating levels of SCFAs

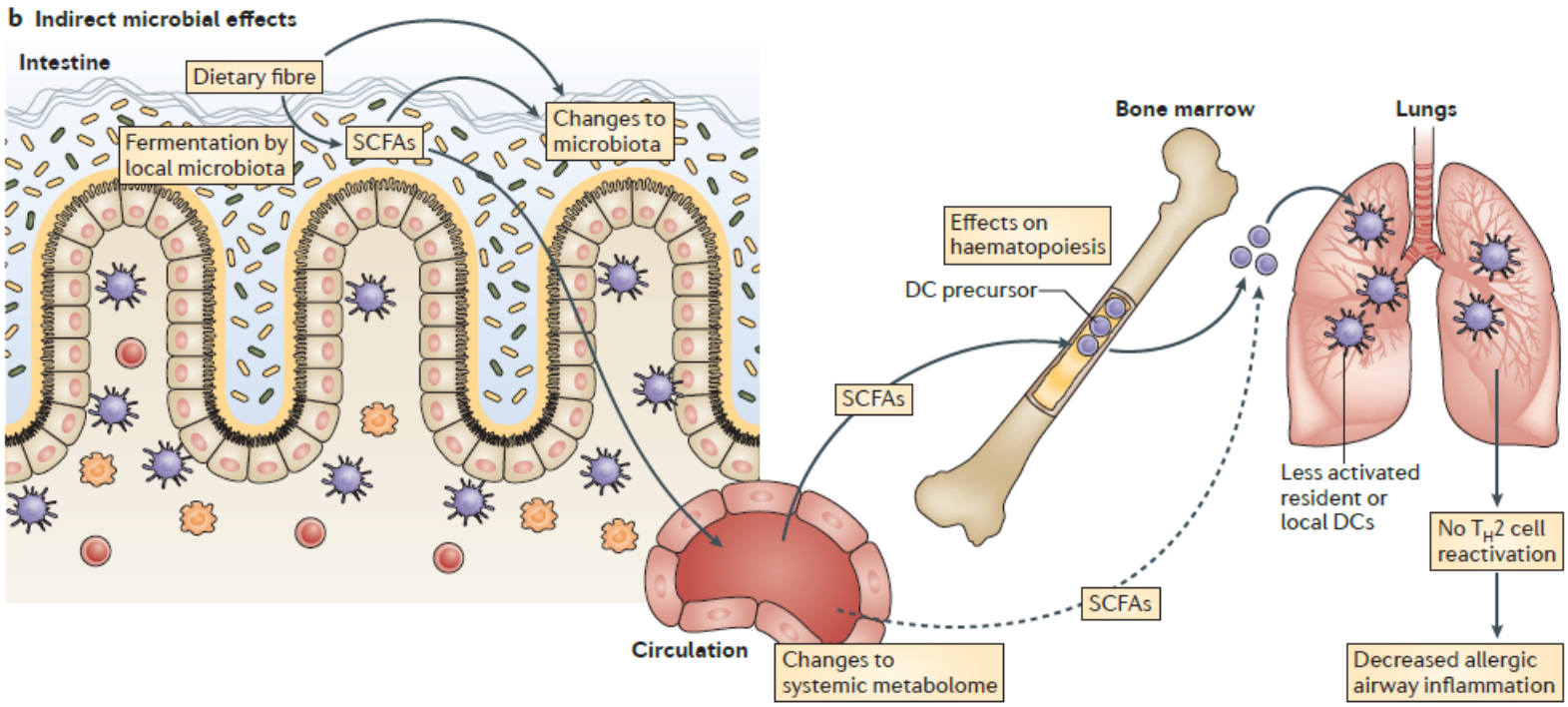






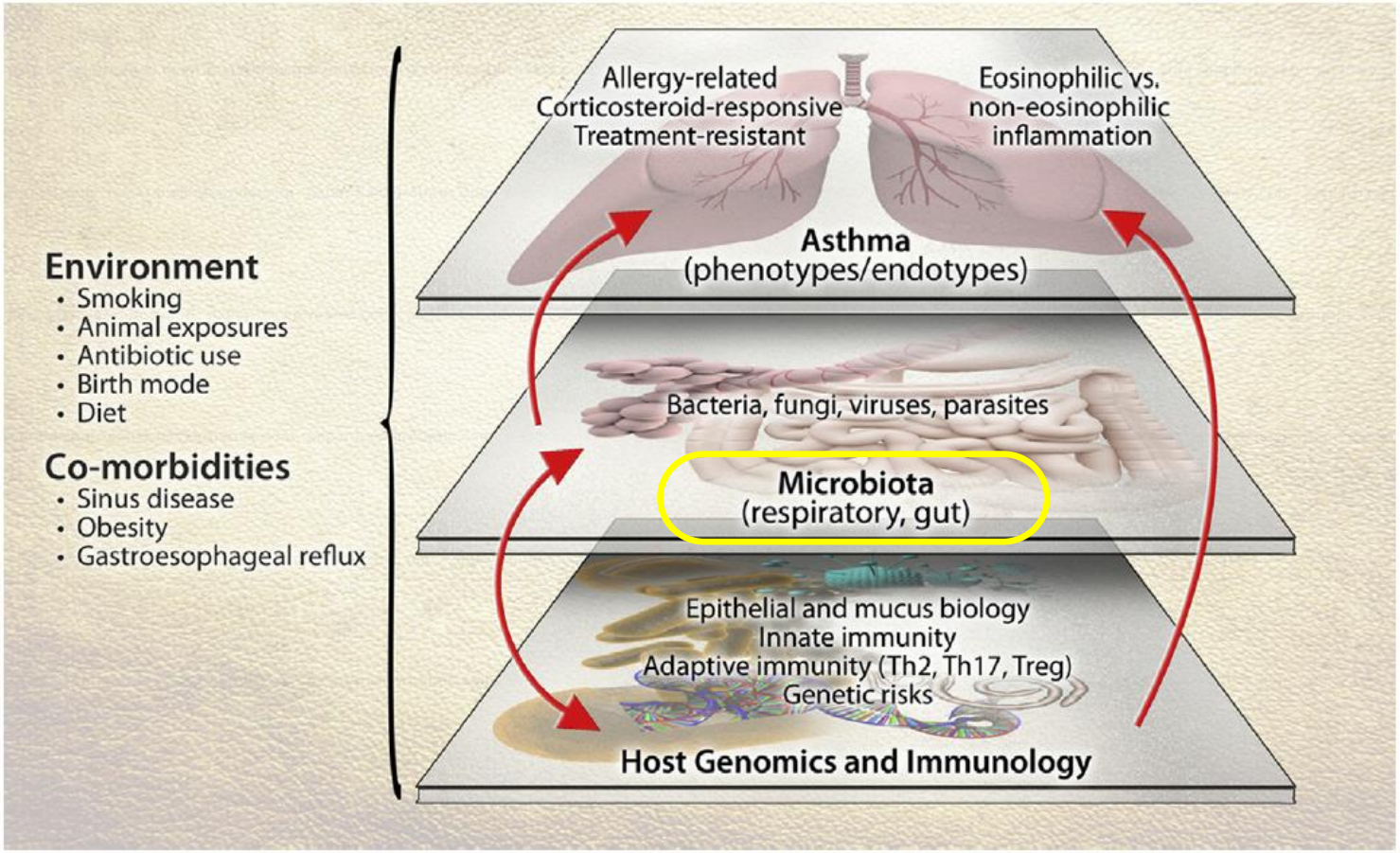
Trompette A et al., Nat Med 2014; 20:159-66

Gut Microbiome: Link between diet and asthma?



Marsland BJ, Gollwitzer ES. Nat Rev Immunol 2014; 14:827-35
Huffnagle GB. Nat Med 2014; 20:120-1

Microbiome and Asthma: Complex Interactions



Huang YJ, Boushey HA. J Allergy Clin Immunol 2015; 135:25-30