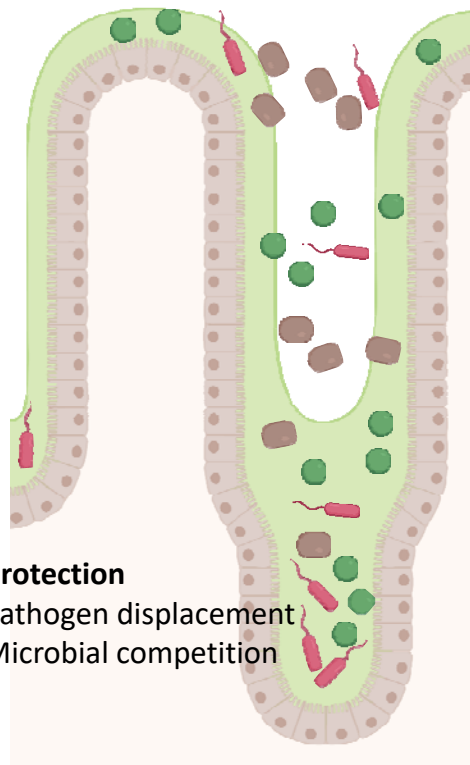# Microbiome & Health

Human microbiome distribution and functions

Human microbiome: microbial ecosystem composed of bacteria, viruses and fungi populating a human host.

Present on every body surface which is exposed to the environment, and every body part with an opening to the environment.
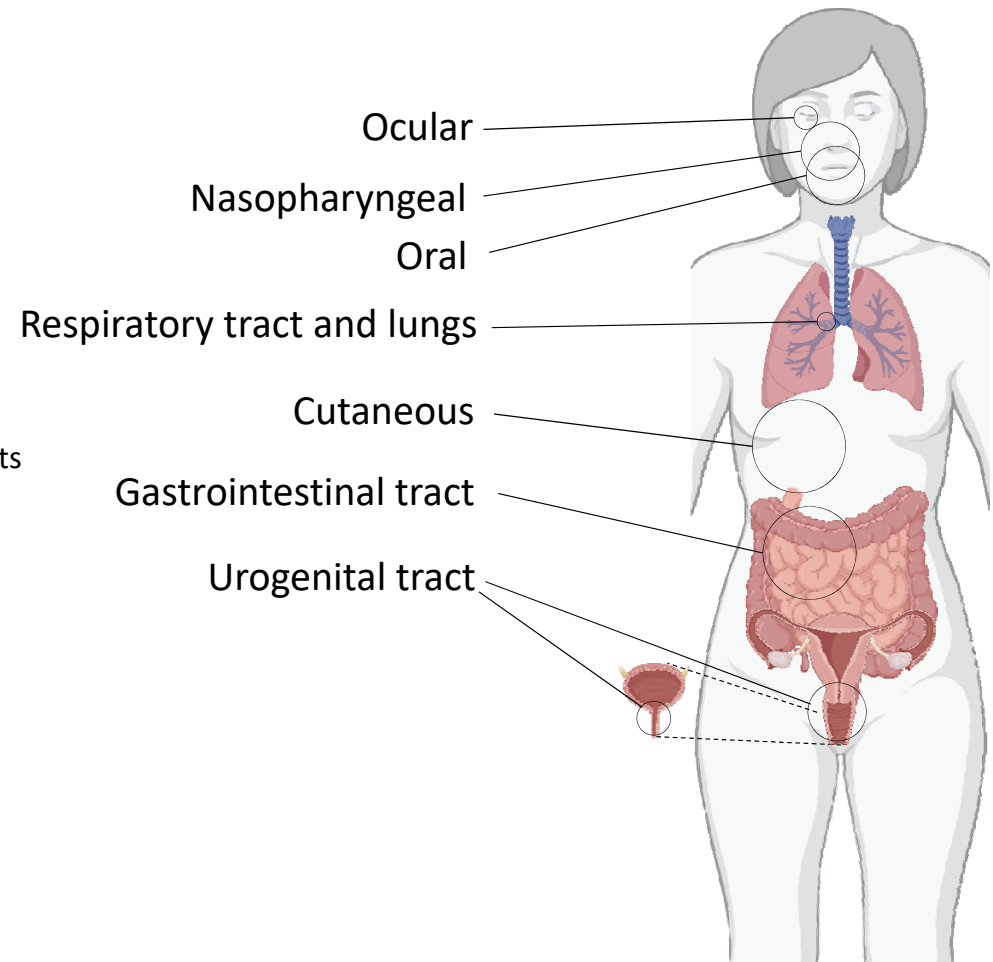
Metabolic functions
Fermentation of non-digestible nutrients
Vitamin synthesis
Salvage of energy
Epithelial cell differentiation
Metabolism of carcinogens

Structure consolidation
Barrier fortification
Immune system development
Induction of IgA and AMPs
Tightening of junctions

Protection
Pathogen displacement
Microbial competition

Ocular
Nasopharyngeal
Oral
Respiratory tract and lungs
Cutaneous
Gastrointestinal tract
Urogenital tract

Definition of a "healthy" microbiome

Conceptual evolution of enteric microbiota colonisation throughout life. Nutritional shifts during lifetime are mirrored by alterations in the composition of the intestinal microbiome.
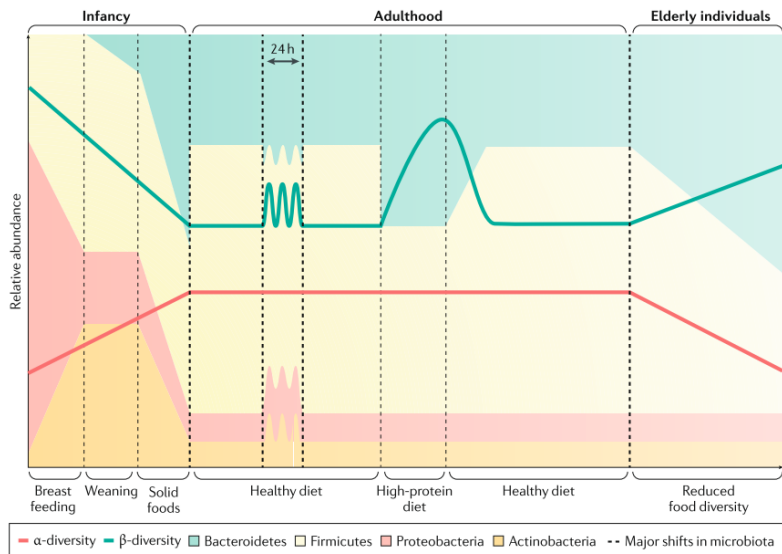
N. Zmora et al. *Nat. Rev. Gastroenterol. Hepatol.* (2019)

Two main attributes to qualify microbiome diversity. α- and β-diversity.

α-diversity describes **richness** and **species diversity** within the same sample composition. Practically:
- How many distinguishable taxa can we count?
- How even are numbers of different taxa? *Shannon index*

β-diversity describes **differences in composition** with **other samples**. Practically:
- How distinct are the species abundances between samples? *Bray-Curtis dissimilarity*
- How much overlap is there in the identity of species between samples? *Jaccard distance*
- How related between themselves are the species identified between samples (phylogenetic relatedness)? *UniFrac*

Definition of a "healthy" microbiome

Microbial communities differ according to body site

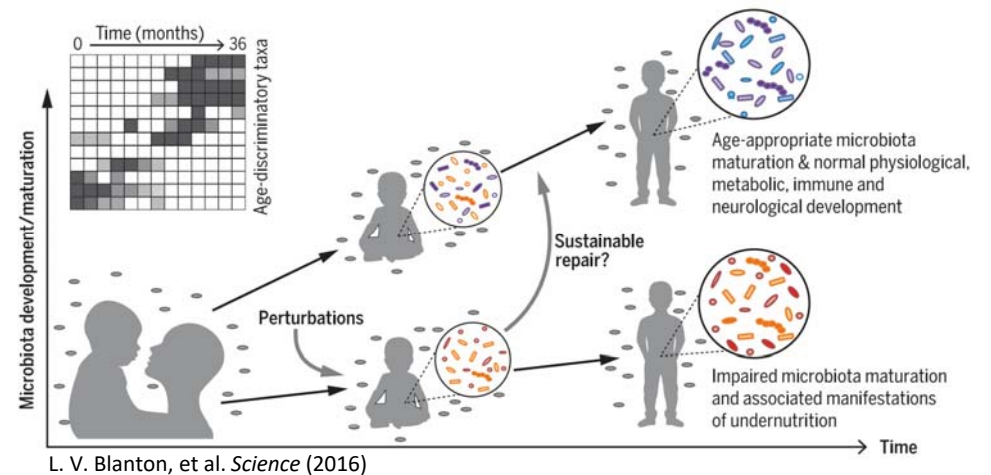The example of the **variability** of cutaneous microbiota
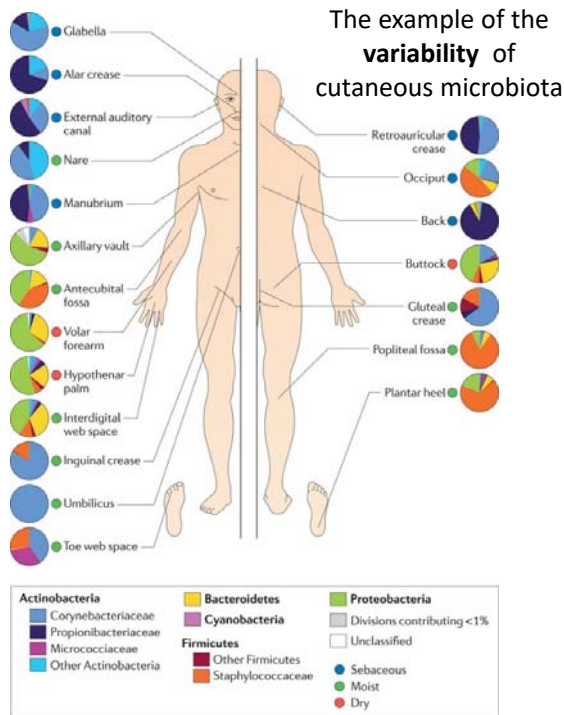
A. L. Byrd, et al., *Nat. Rev. Microbiol.* (2018)

Overall more diversity between individuals than over time

Individual 1, 2,…

time
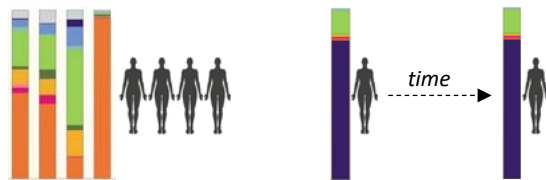
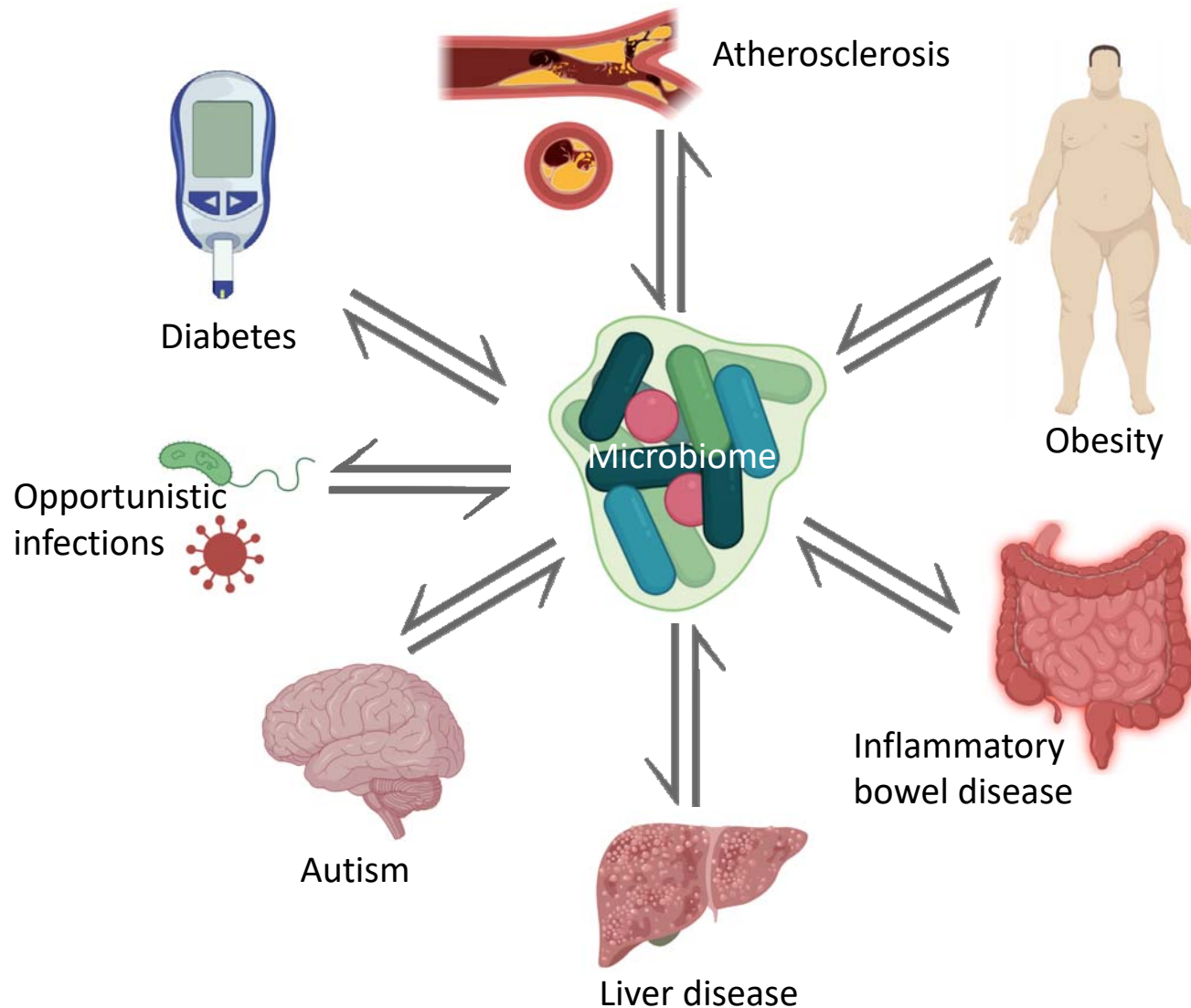Signatures of a healthy microbiome:
Richness and **Diversity**

L. V. Blanton, et al. *Science* (2016)

Highly regulated symbiotic host/microbe relationship based on
- accessing and processing nutrients
- regulating the immune system and immune responses to pathogens
- providing metabolites and neuropeptides regulating energy and behaviour
- mitigating pathogens

Microbiome implication in disease

Atherosclerosis

Diabetes

Opportunistic infections

Autism

Liver disease

Obesity

Inflammatory bowel disease

Microbiome

Chronic diseases such as obesity, inflammatory bowel disease (IBD), diabetes mellitus, metabolic syndrome, atherosclerosis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), cirrhosis, and hepatocellular carcinoma have been associated with the human microbiota

Growing evidence indicates that alterations in the microbiota are implicated in the pathogenesis of a number of other diseases, such as severe asthma, food allergies, autism, and major depressive disorder.

How to study the microbiome in vivo?
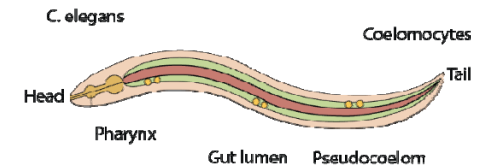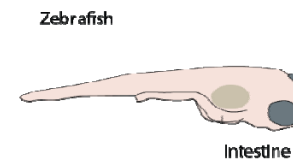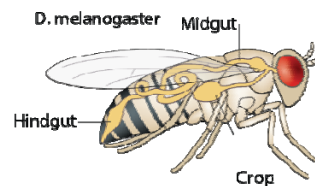
Multi –omics analyses
- Can be applied to humans
- Generates a wealth of knowledge
  - Species identification by sequencing
  - Metaproteomics: identification of all proteins defines functional activity of microbiome
  - Metabolomics: elucidates overall metabolic states of host-microbiome interactions
- Mostly observational
- Challenging to interpret and requiring in-depth statistical analyses

Rodent (Mouse)

Specific bacterial inoculation

Mouse isolator

Non-human primate (Marmoset)
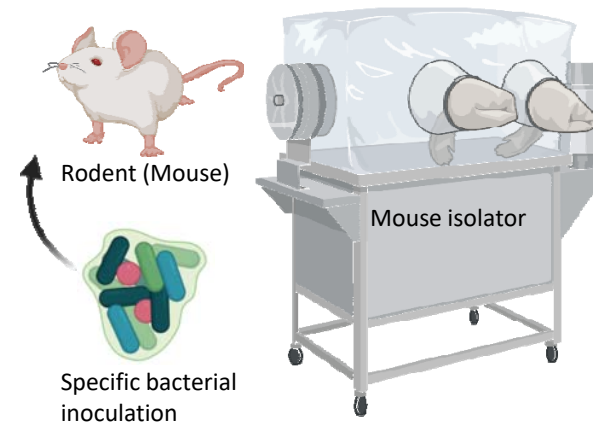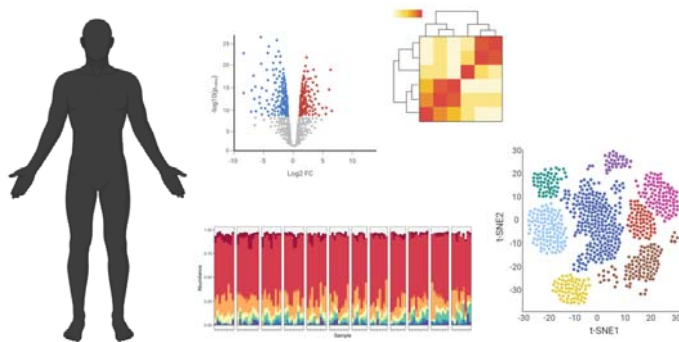
Gnotobiotic animal models
- Allow functional study of the microbiome in a live organism
- Specific bacteria or bacterial ecosystems can be transplanted
- Allows for a controlled environment

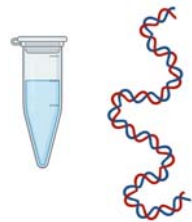Simple animal models for the study of the microbiome

D. melanogaster — Midgut — Hindgut — Crop

Zebrafish — Intestine

C. elegans — Coelomocytes — Tail — Head — Pharynx — Gut lumen — Pseudocoelom

Modified from A. Douglas, *Nat. Rev. Microb.* (2019)

Microbiome techniques: Sequencing
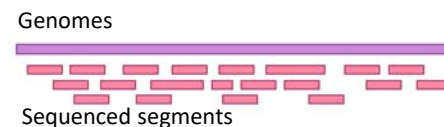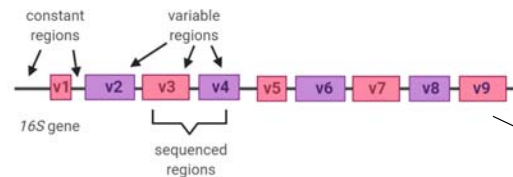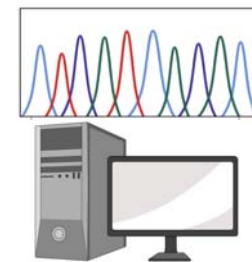
Two major sequencing methods used to determine the microbiota composition
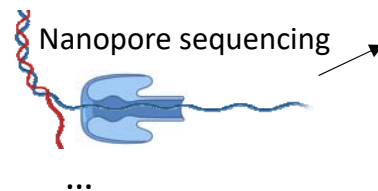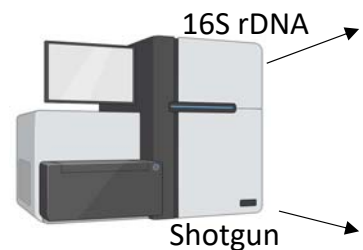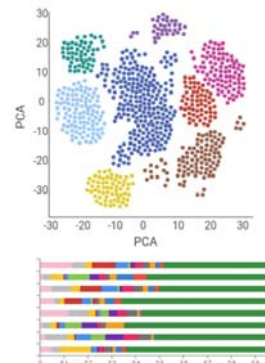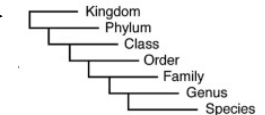- **16S ribosomal DNA sequencing** of specific variable regions (usually V3-V4) which carry sufficient variability to identify distinct bacteria. By far the most used technique. Limited in scope to bacteria.
- **Shotgun sequencing** is based on the fragmentation and sequencing principle, allowing for the identification of all types of organisms
- **Third generation sequencing** including nanopore sequencing and DNA optical mapping and others may provide affordable sequencing options for widespread microbiome tracking

Microbiome oriented therapeutics

Prebiotic: Chemical that induces the growth or activity of microorganisms that potentially contribute to well-being of their host
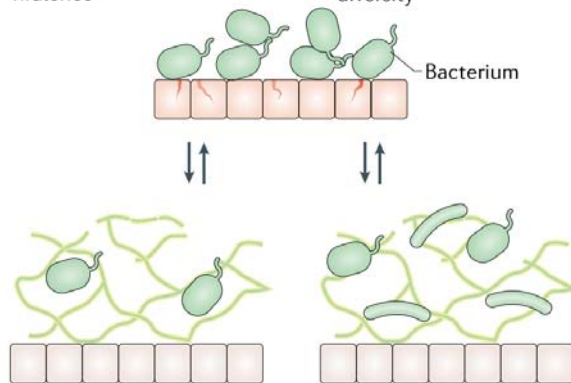
Probiotic: Ingested microorganism(s) associated with beneficial effects to humans and animals

Use of **synthetic mucins**

C. Werlang, et al. *Nat. Rev. Mater.* (2019)

Healthy stool collection　　　**Encapsulation**

Processing
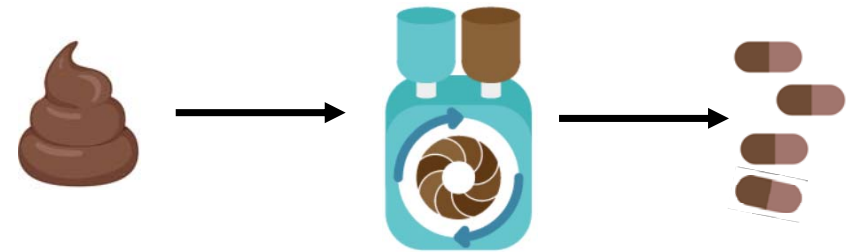
Microbiome transplant:
- **Faecal microbiota transplantation** already used in the treatment of *C.difficile* infections. Great potential for many diseases (Inflammatory bowel disease, obesity, T2D, etc…)
- **Cutaneous microbiota transplantation** is experimental but there is experimental evidence for usefulness in the treatment of acne and atopic dermatitis
- Potentially many other therapeutic applications for different body sites

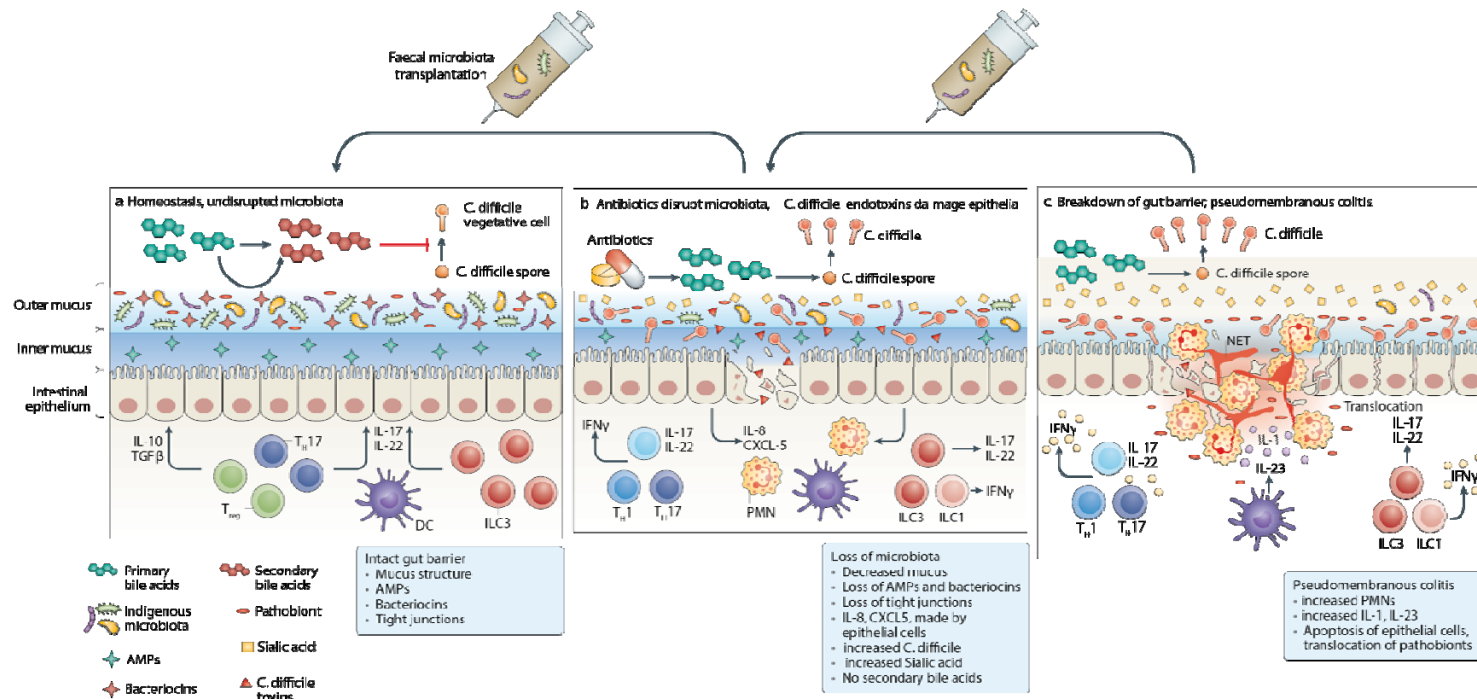# Known mechanisms of microbiome therapeutics

Proposed mechanism of C.difficile colitis and FMT therapeutics

- Primary bile acids metabolised by healthy microbiota inhibit C.difficile
- Antibiotic-induced dysbiosis allows antibiotic-resistant C.difficile germination
- Enterotoxins lead to weakening of tight junctions and

Modified from A. Khoruts, and M. J. Sadowsky, *Nat. Rev. Gastroenterol. Hepatol.* (2016)

Literature referenced and further reading

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4. K. A. Earle et al. Quantitative Imaging of Gut Microbiota Spatial Organization, *Cell Host Microbe* **18**, 478–488 (2015).

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8. C. Werlang, et al. Engineering mucus to study and influence the microbiome, *Nat. Rev. Mater.* **4**, 134–145 (2019).

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