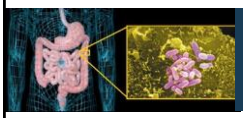
UNIVERSITEIT GENT

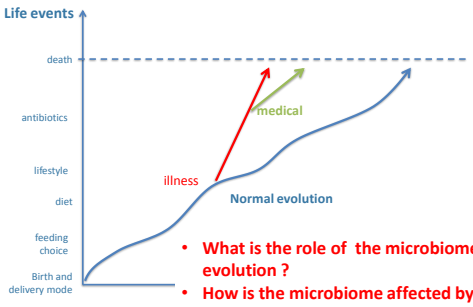


Interactie van voeding met het darmmicrobioom: sleutel tot de menselijke gezondheid

Tom Van de Wiele
CMET - Center for Microbial Ecology and Technology
Ghent University

FLANDERS' FOOD, May 12th 2017

Evolution of health



- **What is the role of the microbiome in health evolution ?**
- **How is the microbiome affected by diet ?**

Introducing the human microbiome

The black box of host microbiome research

How to select a "healthy" microbiome ?

" You are what you eat " ???

- Life events
- Life style
- Dietary habits
- Antibiotic use
- Disease
- …

→ Reality is more complex

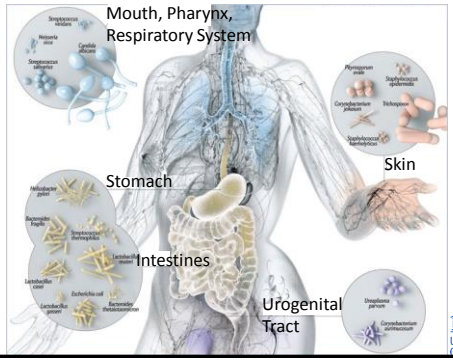
Human evolution took place in a microbial world

Planet earth	4.5 billion yr
Micro-organisms	3 billion yr
Mammals	200 million yr
Humanoid	2 million yr
Homo sapiens sapiens	200.000 yr

19 evolutionary steps to make a human

We are born into a microbial world

Our body harbors microbial worlds

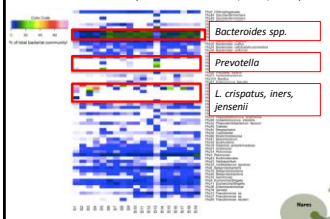


You form a minority group in your own body

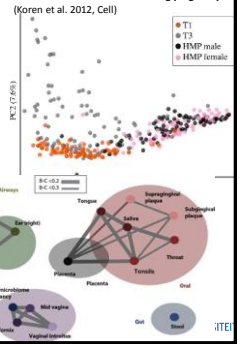
- N° cells in body :
  - 10% human
  - 90% bacterial
- N° genes:
  - 1% human
  - 99% bacterial

Determinants of a newborn's microbiome

The uterine microbiome (Verstraelen et al. 2016, PeerJ, CMET)

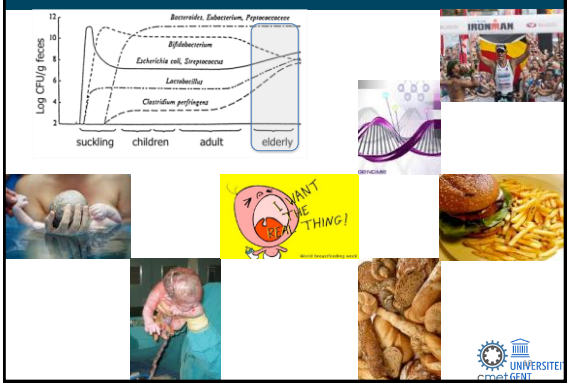


Maternal microbiome shifts during pregnancy
(Koren et al. 2012, Cell)

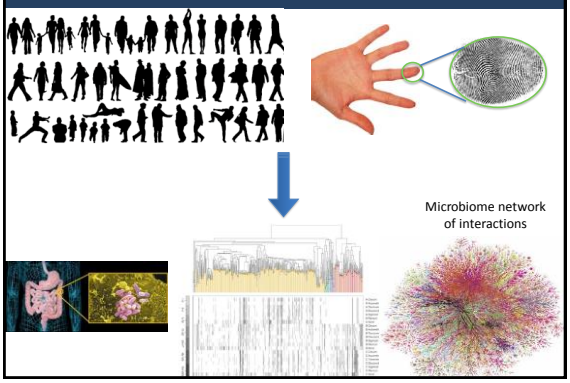


The placental microbiome
(Aagaard et al., 2014, Sci, Transl Med)

The microbiome evolves within 1 individual



… leading to a unique microbial identity…



… with similar functionality …

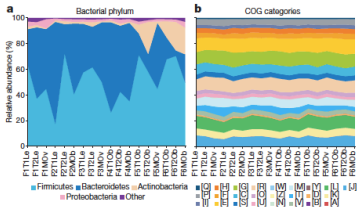
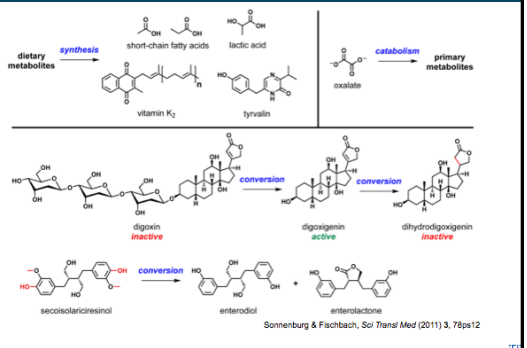


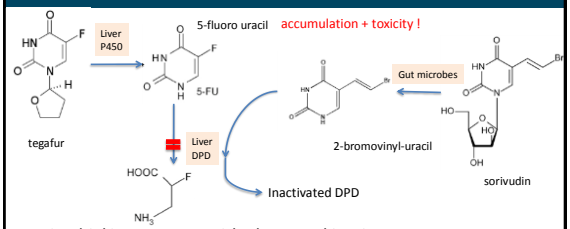
Figure 3 | Comparison of taxonomic and functional variations in the human gut microbiome. **a**, Relative abundance of major phyla across 18 faecal microbiomes from monozygotic twins and their mothers, based on BLASTX comparisons of microbiomes and the National Center for Biotechnology Information non-redundant database. **b**, Relative abundance of categories of genes across each sampled gut microbiome (letters correspond to categories in the COG database).

Turnbaugh et al., 2008

… an enormous metabolic potential (>> liver !)…



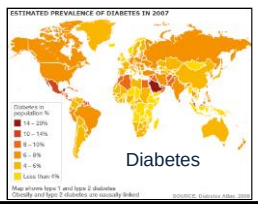
… but sometimes far-reaching consequences.

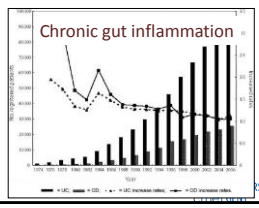


Microbial interference with pharmacokinetics

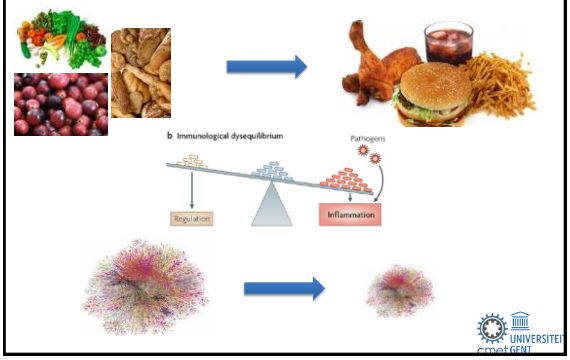
- Tegafur: Chemotherapy prodrug for colorectal cancer
- Sorivudin: Antiviral agent
  - Microbial metabolism interferes with 5-FU clearance
  - Toxicity: 18 casualties in Japan (Okuda et al., 1998)
  - Requirement for patient screening on DPD sensitivity to microbes

However…

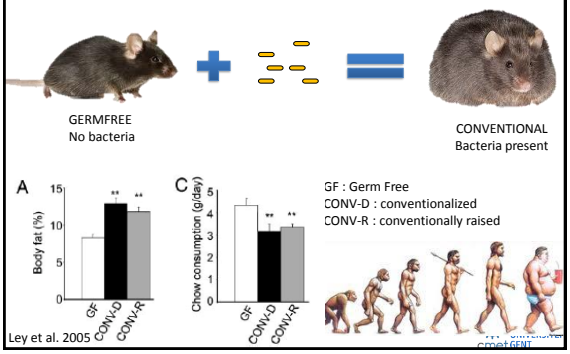




Dietary shifts as contributor to microbial dysbiosis

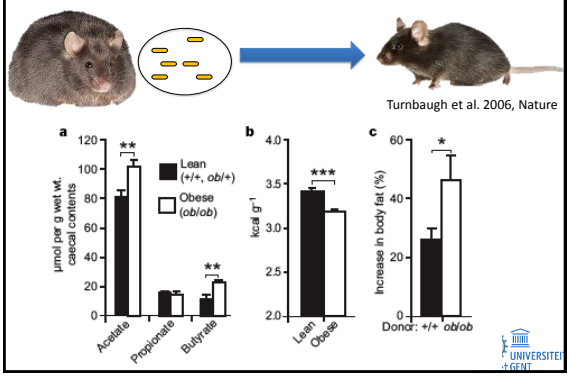


Presence of bacteria triggers body fat



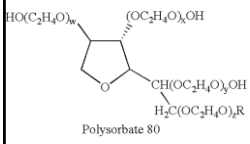
Ley et al. 2005

Obese microbiota trigger obesity in lean mice !

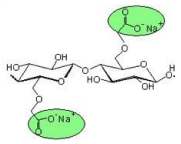


Chemical emulsifiers in western-style diets



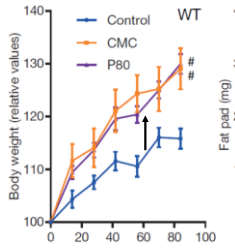
Polysorbate 80

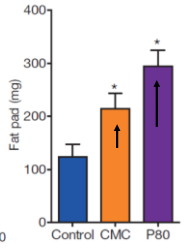


carboxymethylcellulose

Polysorbate 80

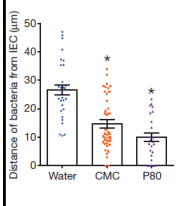
Chemical emulsifiers increase fat mass and body weight



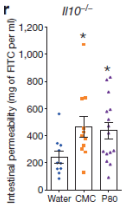


Chassaing et al. 2015. Nature
Chassaing et al., 2017. Gut. CMET

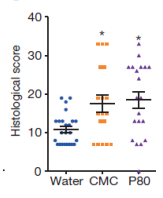
Chemical emulsifiers :
- lower microbial distance to epithelium
- compromise gut barrier function
- increase inflammation



Distance to epithelium ↓



Impaired gut barrier



Increased inflammation

Other risk factors: antibiotic resistance → search for novel antimicrobials ?

WHO's first global report on antibiotic resistance reveals serious, worldwide threat to public health

New WHO report provides the most comprehensive picture of antibiotic resistance to date, with data from 114 countries

News release

World Health Organization

Deaths attributable to antimicrobial resistance every year by 2050

Melk van Tasmaanse duivels doodt resistente bacteriën

DE REDACTIE.BE

Antibiotic resistance: World on cusp of 'post-antibiotic era'

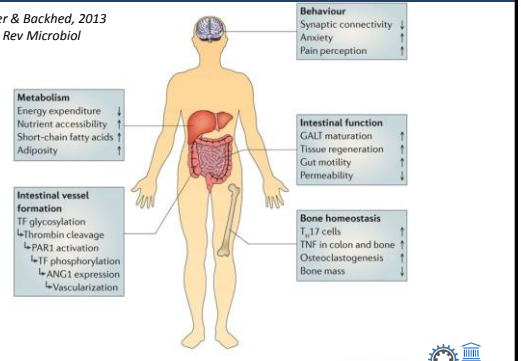
By James Gallagher
Health editor, BBC News website

19 November 2015 Health

Source: The Review on Antimicrobial Resistance

Impact of the microbiome on human physiology

Sommer & Backhed, 2013
Nature Rev Microbiol



Nature Reviews | Microbiology

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Introducing the human microbiome

The black box of host microbiome research

How to select a "healthy" microbiome ?

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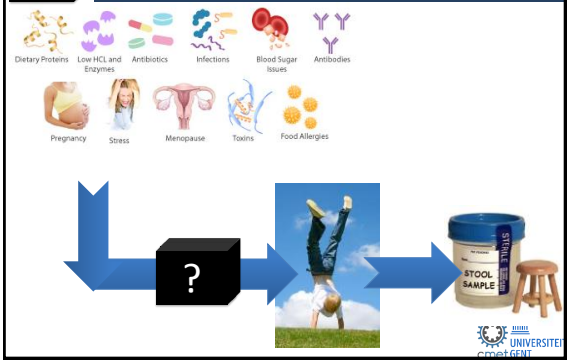
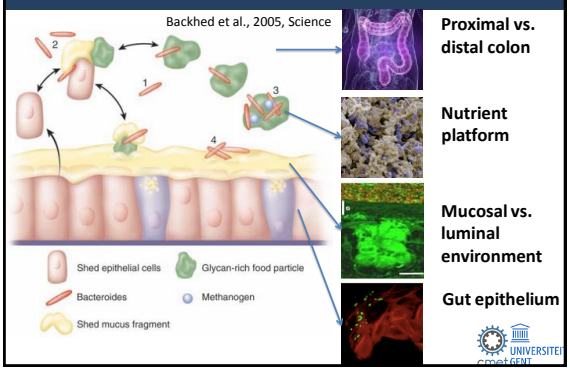
The black box in host microbiome research



There is no such thing as "the" microbiome



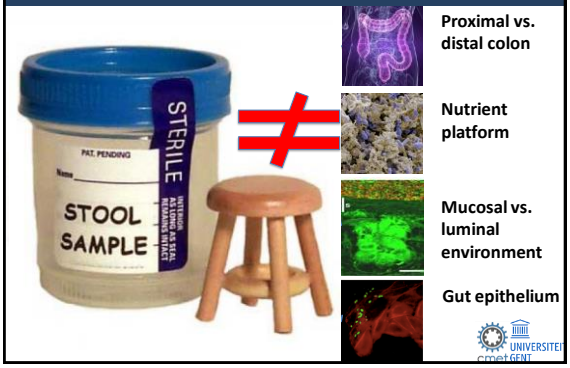
Proximal vs. distal colon

Nutrient platform

Mucosal vs. luminal environment

Gut epithelium

Micro-environment differences



Proximal vs. distal colon

Nutrient platform

Mucosal vs. luminal environment

Gut epithelium

In vitro enabling technologies

SHIME: Simulator of the human intestinal microbial ecosystem
mucosal-SHIME, Host Microbe Interaction Module…

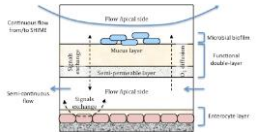
CMET publications

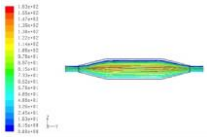
Molly et al. (1994); Possemiers et al. (2006) J Nutr, Van den Abbeele et al. (2013) ISME J, Marzorati et al (2014) BMC

Microcosms

Coated with mucin type II-agar

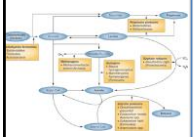
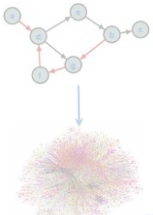
9 mm



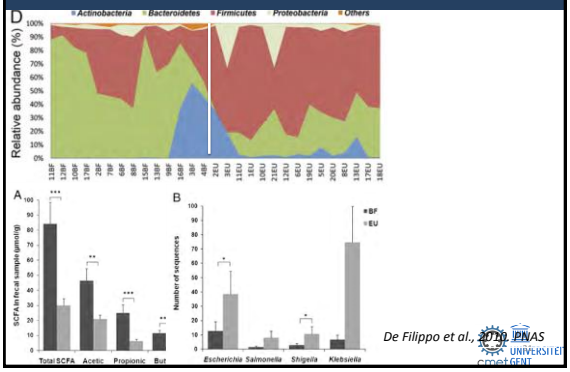


- Introducing the human microbiome
- The black box of host microbiome research
- How to select a “healthy” microbiome ?

Strategies

Diet	(future) probiotics	Ecosystem restoration
		
	Single or mix	
		

1. Fiber rich diets increase healthy microbes

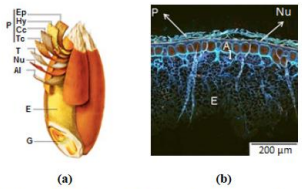


De Filippo et al., 2010, PNAS

Sources of dietary fiber

- Fruits, vegetables, whole grains…

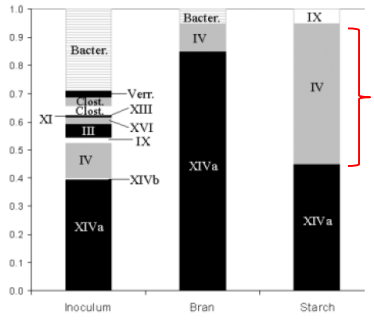
→ Focus on whole grain foods: wheat bran, arabinoxylans, arabinogalactan…



Fiber per 100 g of grain	
wheat	12 g
oats	10.6 g
rye	14.6 g
corn	7.3 g
brown rice	3.5 g
refined wheat	<2 g
white rice	<2 g

Figure 3.5. Presentation of the pericarp (P) [(epidermis (Ep), hypodermis (Hy), cross - (Cc) and tubular cells (Tc)], the testa (T), the nucellar epidermis (Nu) and the aleurone (Al) of bran that surround the starchy endosperm (E) and the germ (G) of the wheat grain (a). Fluorescence microscopy picture of cross-section of bran whereby cell walls (in blue, Calcofluor) and proteins (in red, Acid Fuchsin) were stained and starch appears in black (b). Scanning Electron Microscopy image of a cross section of bran (c) [9] **Van Craeyveld et al., 2010; Jerkovic et al., 2010**

Unfermentable fiber as mirobial colonization site

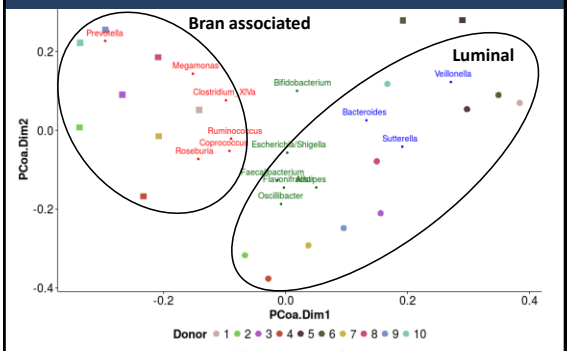


Ruminococcus bromii and starch fermentation

Rowett Research Institute

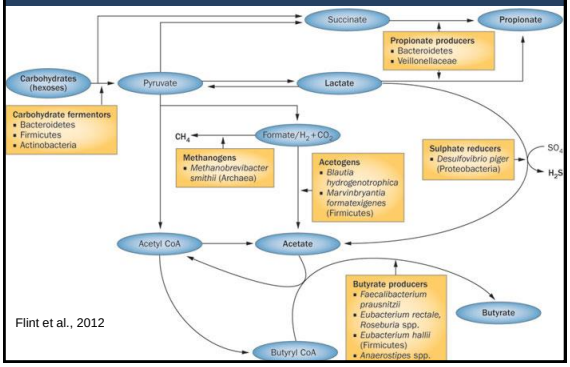
Leitch et al. 2007

Preferential adhesion of bran by microbiota from the gut



De Paepe et al., 2017, submitted

Fiber facilitates microbial interactions: especially **butyrate** production



Flint et al., 2012

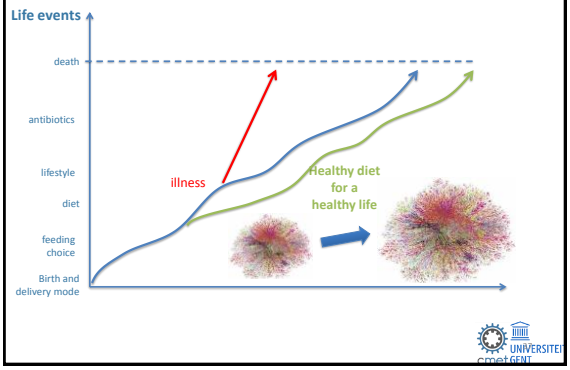
Health impact of dietary fiber ?

De Vries et al., 2015. World J. Gastroenterol.

Physiological properties	reference
Additional energy source	Cummings et al. 1997
Increased satiety	Haber et al. 1977
Control of blood glucose and insulin	Haber et al. 1977
Cholesterol lowering	Fiordaliso et al. 1995
Bile acid dehydroxylation	Munster et al. 1994
Laxative	Cummings et al. 1993
Fecal bulking and improved bowel transit	Phillips et al. 1995
Bifidogenic	Gibson et al. 1995
Improved colon epithelial functioning	Roediger 1980; Cummings et al. 1995
Microbiome modulation	∞

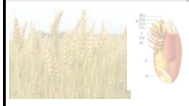
Physiological / microbial effects → Health effects ? (EFSA)

Food innovation for improved evolution of health



Strategies

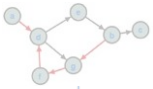
Diet



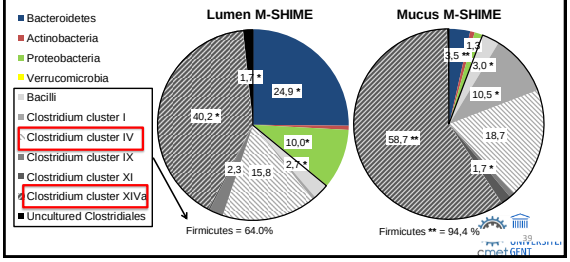
(future) probiotics

Single or mix

Ecosystem restoration



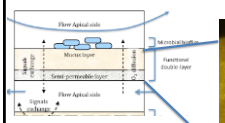
Healthy mucosal microbiome: preferential colonization by butyrate producing Clostridium clusters IV and XIVa



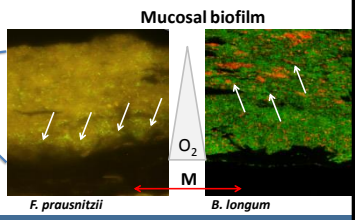
Butyrate producing Clostridia preferentially colonize mucus

e.g. F. Prausnitzii

- Downregulated in Crohn's disease / ulcerative colitis

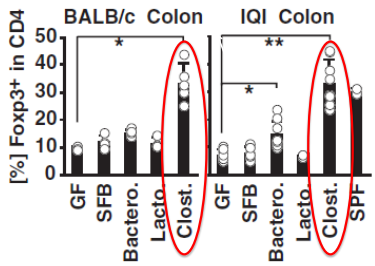


Marzorati et al., 2014, *BMC, LabMET*



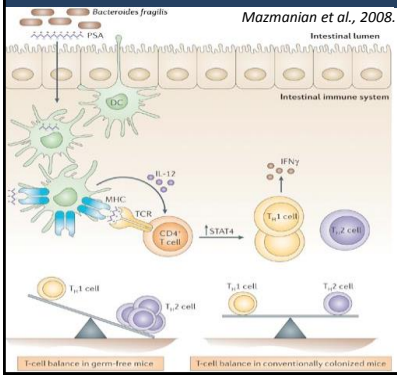
Faecalibacterium prausnitzii copes with mucosal oxidative stress

Butyrate producers stimulate immune system



Atarashi et al., Science, 2011

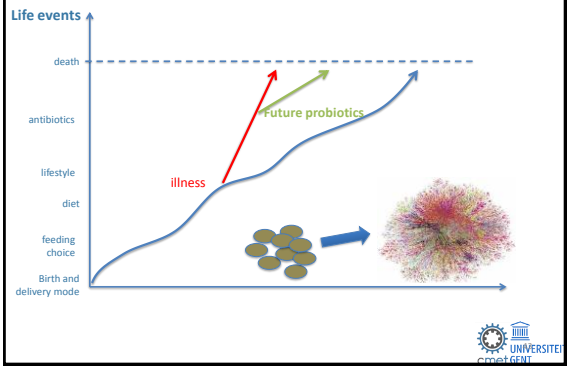
PSA from B. fragilis stabilizes the immune balance



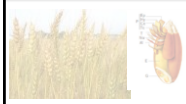
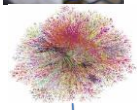
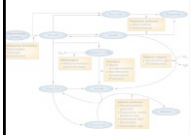
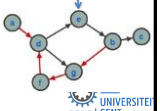
Mazmanian et al., 2008. Nature

Bacteroides fragilis: **stimulation of cell-mediated immunity**

Novel probiotics for therapeutic medicin



Strategies

Diet	(future) probiotics	Ecosystem restoration
		
	Single or mix	
		

Strategy 3: ecosystem restoration

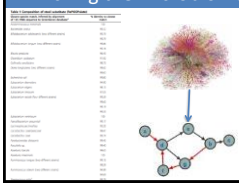
Fecal Microbial Transplants

+ Success rate:
  - *C difficile* infections: often superior to antibiotics
  - Other diseases: scarce literature

However:
- Badly characterized
- Infection transmission
- Mode of action: unknown

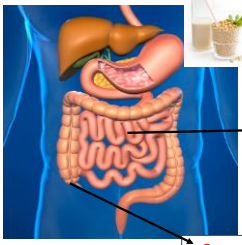
→ No longterm future

Mimicking the microbiome with miniature ecosystems



+ Phylogenetic diversity (not just LAB !)
+ Mode of action known
+ Perfectly characterized
+ Specialized ecosystems for specific pathologies
+ Technically reproducible
− Regulatory update required

Case study on dietary linoleic acid : how to tease out microbial ecological stabilizers

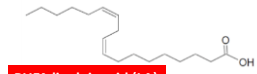


Fat digestion and absorption in the small intestine
= very efficient (± 95%)

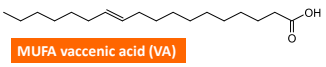
Crohn's disease, malabsorption diseases, anti-obesity drugs

Several grams of linoleic acid in the colon per day

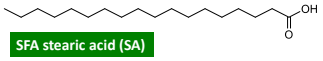
Bioactivity of linoleic acid in the colon: (1) antimicrobial effects and (2) biohydrogenation



PUFA linoleic acid (LA)



MUFA vaccenic acid (VA)



SFA stearic acid (SA)

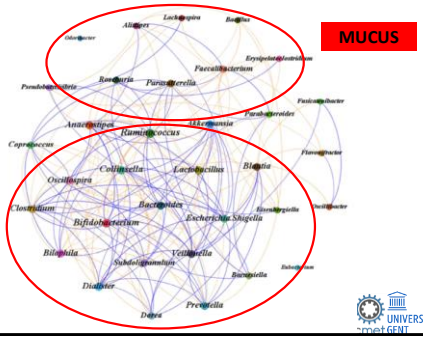
$+ H_2$

Antimicrobial activity decreases!

Active biohydrogenators

Pseudobutyrivibrio
Roseburia

Correlation network for control samples reveals 2 groups: Large luminal network vs. smaller mucosal network (containing butyrate producers)

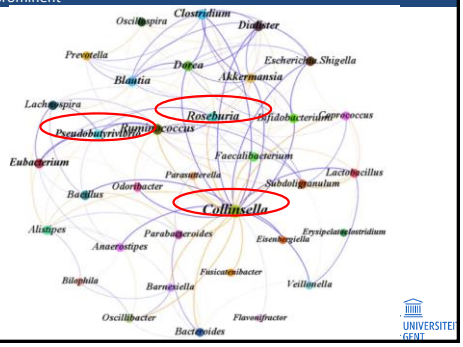


MUCUS

LUMEN

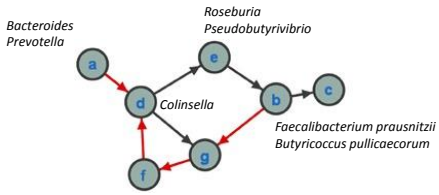
Linoleic acid stress:

Hydrogen producing *Collinsella* and mucosal biohydrogenating *Pseudobutyrivibrio* and *Roseburia* become more prominent

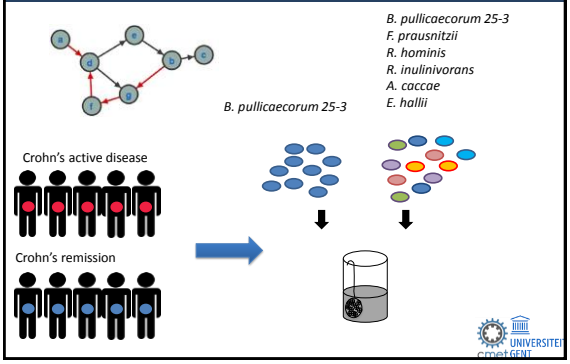


Network identification: collaborome

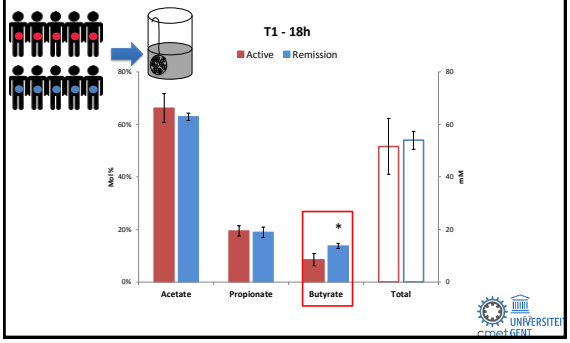
"a functionally active network of collaborating microorganisms"



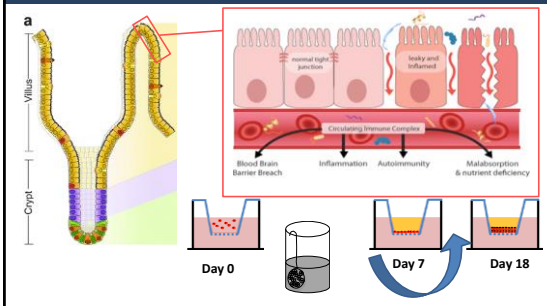
Ecosystem restoration : cocktails of butyrate producers



Active crohn's vs remission : 35% lower butyrate production concomitant decrease in F. prausnitzii

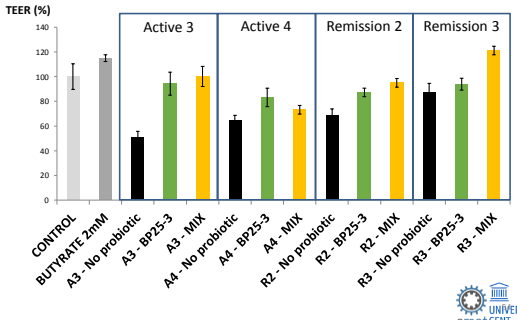


Epithelial barrier function: Addition of M-SHIME intestinal water during differentiation process

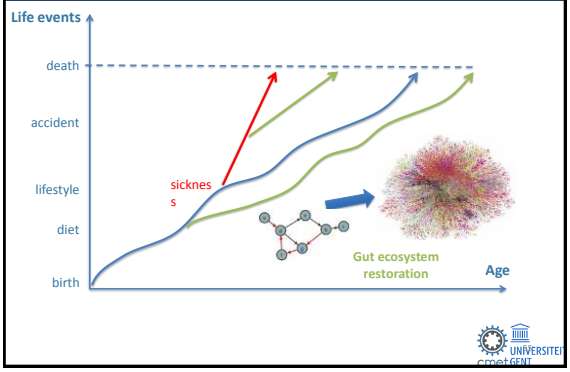


Transepithelial electrical resistence (TEER) as measure For epithelial barrier function

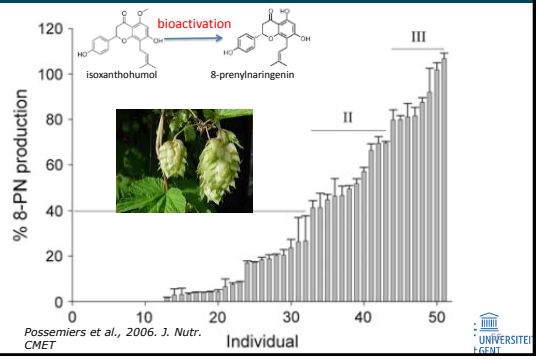
Butyrate producers strengthen barrier function



Future therapy : Gut ecosystem restoration
Microbial Medicinal Products: preventive and therapeutic



THE challenge:
understanding interindividual variability



Possemiers et al., 2006. J. Nutr.

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