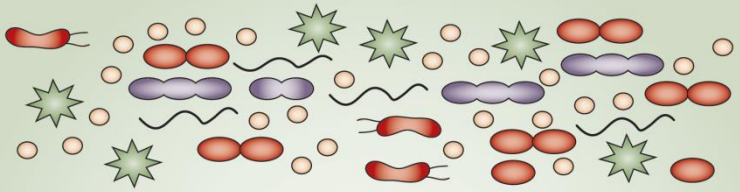
Role of the gut microbiota in over- and undernutrition

Laure Bindels, PhD
Copenhagen
September 7, 2016

Diet
Nondigestible carbohydrates
Fat

Gut microbiota



Changes in microbial metabolism
Saccharolytic activity
Production of bile acids
…
Changes in composition (phylogenic)
Phyla: Bacteroidetes and Firmicutes
Class: Mollicutes
Species or genera:
Bifidobacteria
Faecalibacterium prausnitzii
Lactobacilli
…

Adapted from Delzenne *et al.*, Nat Rev Endocrinol 2011

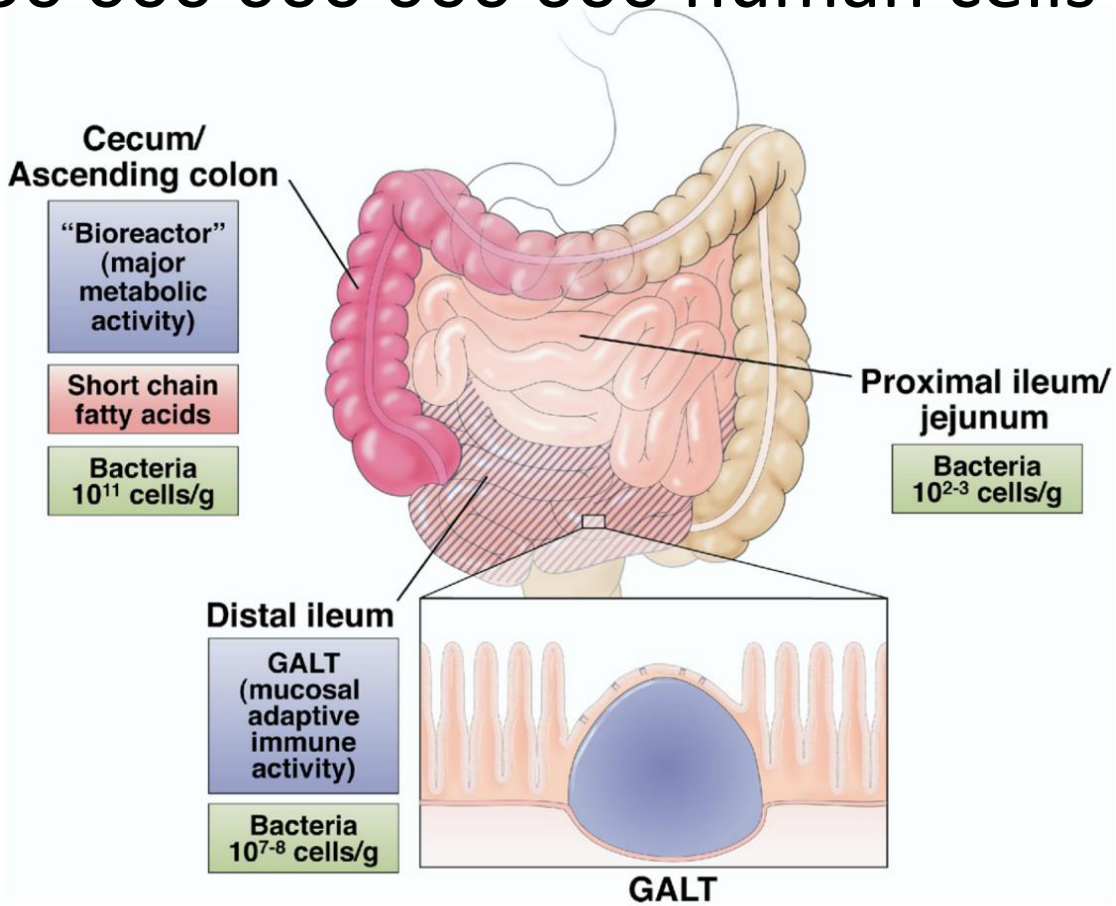
Outline

1. Gut microbiota as a nutritional target
2. Metabolic disorders associated with obesity
3. Metabolic disorders associated with cancer
4. Gut microbiota in alcohol-dependent patients

The gut microbiota

40 000 000 000 000 microbes

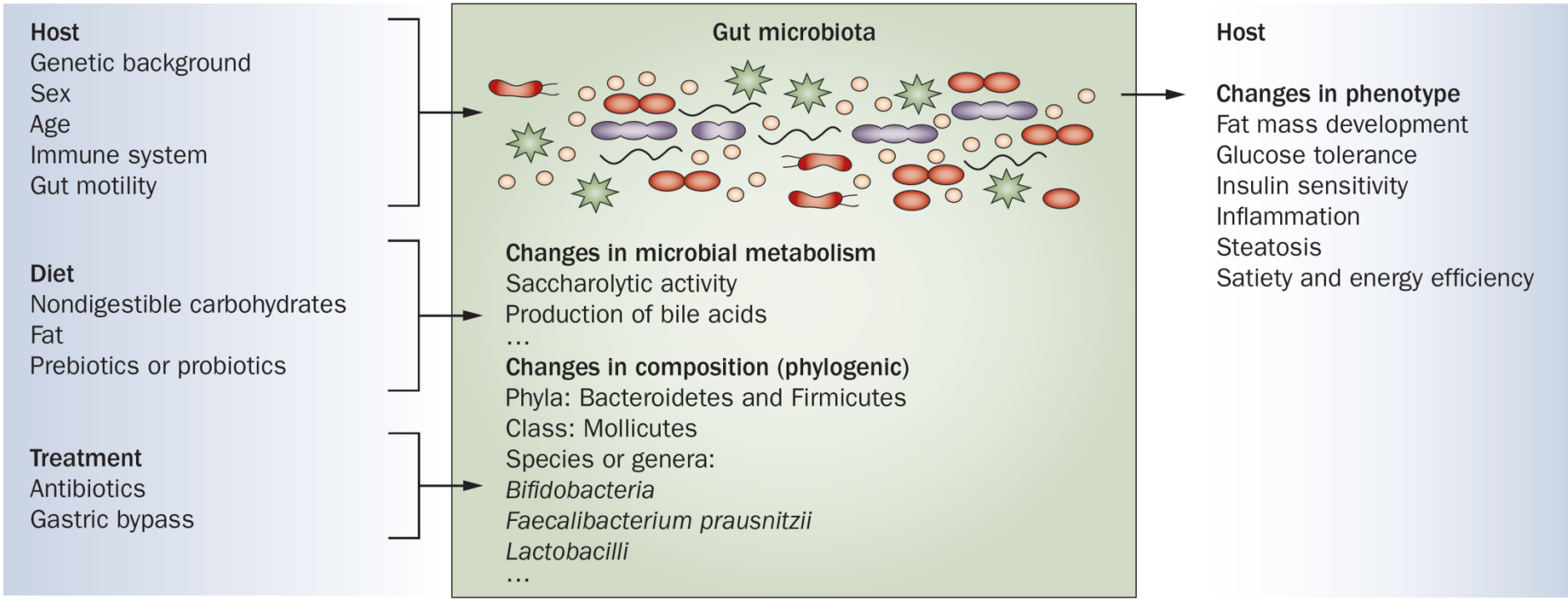
30 000 000 000 000 human cells



for a 'reference man' (70 kilograms, 20–30 years old and 1.7 meters tall)

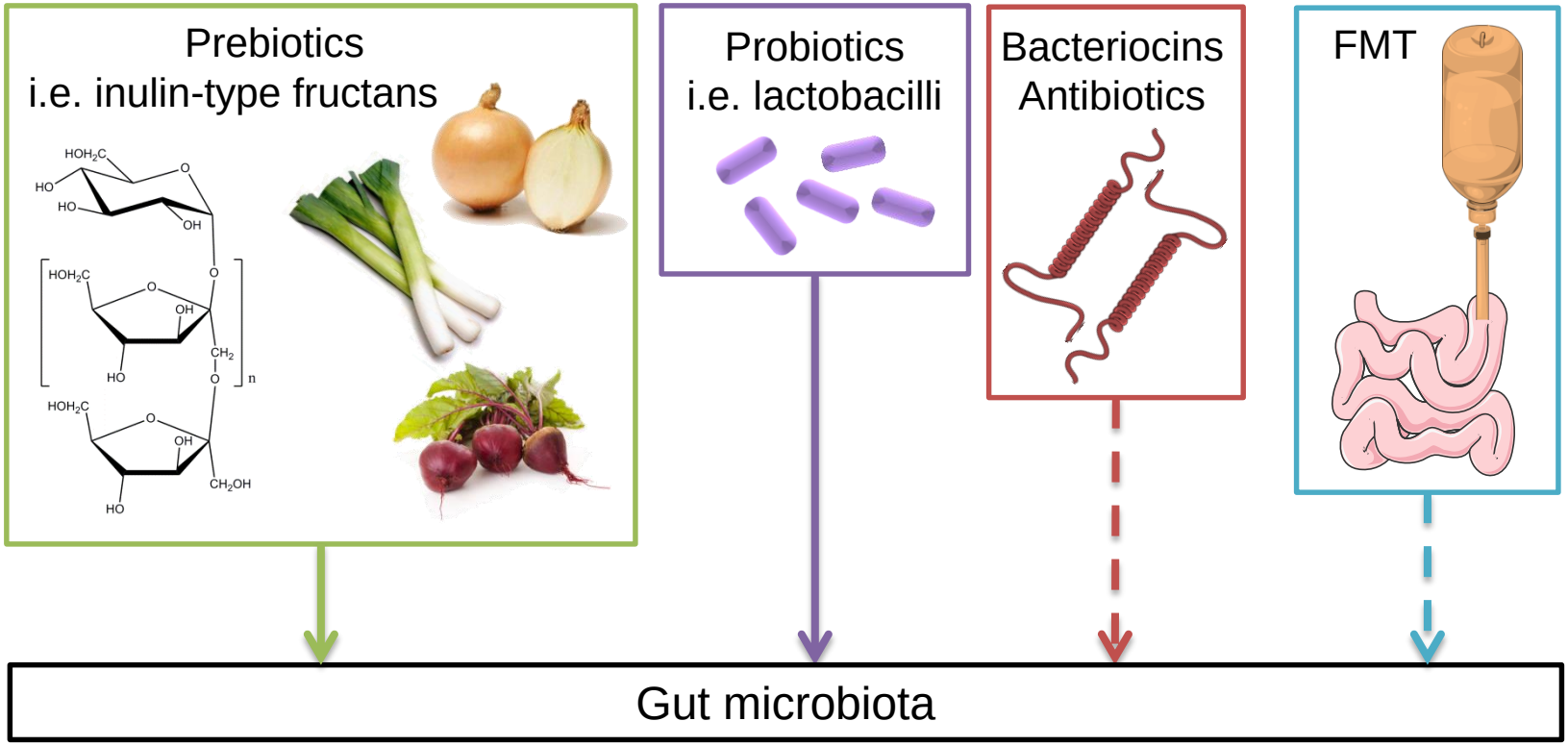
Numbers from Sender et al, preprint on bioRxiv, 2016. Neish, Gastroenterology 2009

Gut microbiota-host crosstalk



Delzenne *et al.*, Nat Rev Endocrinol 2011

1



Experimental tools to study our microbial partners

Adapted from Bindels & Delzenne, Int J Biochem Cell Biol 2013

1

Prebiotics

Dietary Modulation of the Human Colonic Microbiota: Introducing the Concept of Prebiotics

GLENN R. GIBSON AND MARCEL B. ROBERFROID[*1]

MRC Dunn Clinical Nutrition Centre, Cambridge, United Kingdom and
**Unité de Biochimie Toxicologique et Cancérologique, Département des Sciences Pharmaceutiques, Université Catholique de Louvain, Brussels, Belgium*

Beneficial physiological effects

Gibson & Roberfroid, J Nutr 1995

Future research on prebiotics

	Definition	Substantiation of prebiotic effect	Compounds
2010	A selectively* fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health[52]	Selectivity of effect on gut microbiota should be established *in vivo* using most up-to-date technology Health effects, or at least physiological effects, should be established in controlled trials and correlated with selective changes in gut microbiota composition or activity	Inulin FOS tGOS Lactulose
2015	A nondigestible compound that, through its metabolization by microorganisms in the gut, modulates composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host	The degree to which the effect of the prebiotic on composition and/or activity is "selective" is not a criterion The burden of proof for health claims does not change Definition places more focus on the causal link between the microbial metabolization of the compound, the resulting modulation of the gut microbiota, and the beneficial physiological effects	Inulin FOS tGOS Human milk oligosaccharides **Candidate prebiotics?‡** ▪ Resistant starch ▪ Pectin ▪ Arabinoxylan ▪ Whole grains ▪ Various dietary fibres ▪ Noncarbohydrates that exert their action through a modulation of the gut microbiota

Nature Reviews | Gastroenterology & Hepatology

Figure 1 Current and proposed definitions for the concept of prebiotics

Bindels et al, Nat Rev Gastroenterol Hepatol 2015

Resistant starches

Resistant starches (RS) include all starch and starch degradation products not absorbed in the small intestine of healthy individuals.

TABLE 1 Types of resistant starches[1]

Designation	Description	Example
RSI	Physically inaccessible starch	Coarsely ground or whole-kernel grains
RSII	Granular starch with the B- or C-polymorph	High-amylose maize starch, raw potato, raw banana starch
RSIII	Retrograded starch	Cooked and cooled starchy foods
RSIV	Chemically modified starches	Cross-linked starch and octenyl succinate starch
RSV	Amylose-lipid complex	Stearic acid-complexed high-amylose starch

[1] RSI, type I resistant starch; (RS); RSII, type II resistant starch; RSIII, type III resistant starch; RSIV, type IV resistant starch; RSV; type V resistant starch.

Asp, Trends Food Sci Technol, 1992; Birt et al., Adv Nutr 2013; Martinez et al, Plos ONE 2010.

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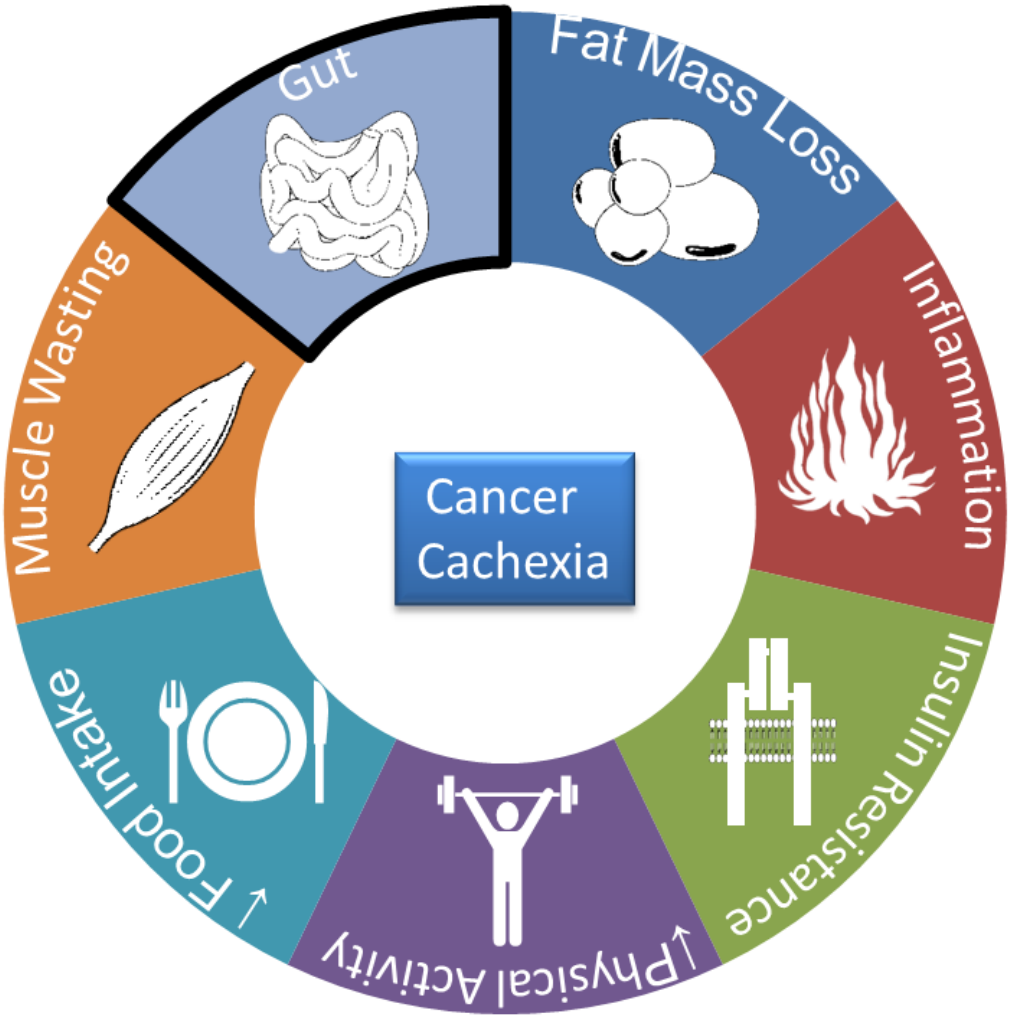
Cancer cachexia



Bindels & Thissen, Clin Nutr Exp 2015

Cancer cachexia

- Up to 80% of cancer patients, depending of the tumor site
- Reduces quality and length of life
- May be a cause of cancer therapy discontinuation
- No valid treatment

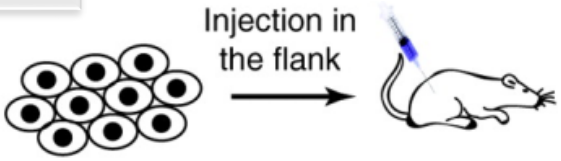
Giacometti, Walking man

Fearon *et al.*, Cell Metab 2012; Fearon et al., Nat Rev Oncol 2013; Argiles et al, Nat Rev Cancer 2014.

A microbial signature in cancer cachexia

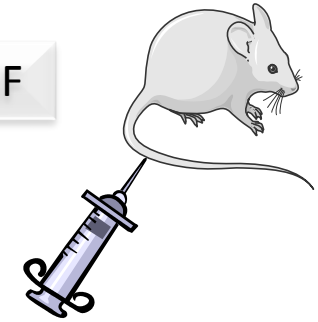
Community-wide approach to characterize the gut microbiota in two mouse models of cancer cachexia

C26



C26 colon carcinoma cells

BaF

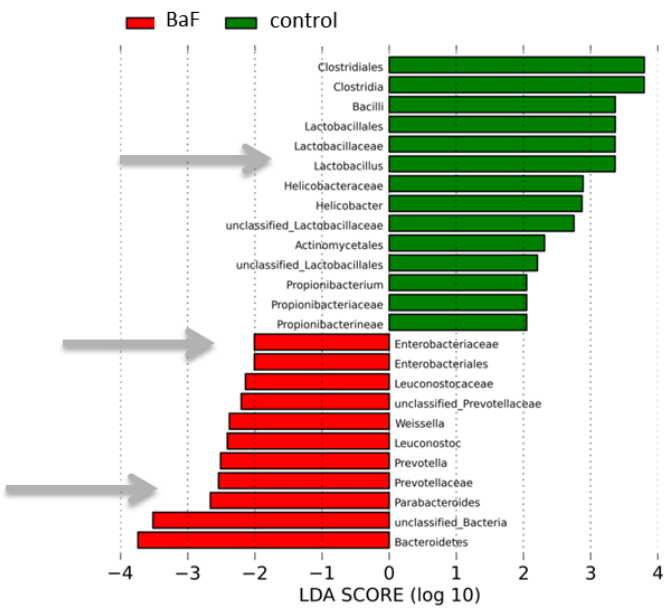


BaF3 cells with Bcr-Abl

Bindels et al, The ISME J 2016

A microbial signature in cancer cachexia

BaF



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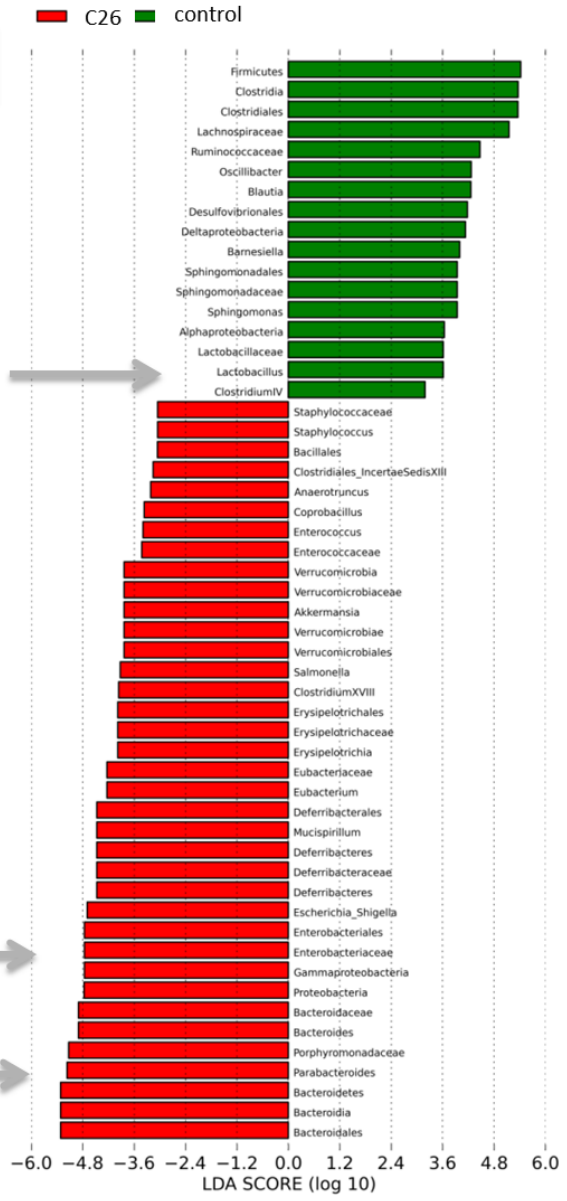


16S rRNA genes from the caecal microbiota analysed by Illumina MiSeq.
Logarythmic LDA score.

↑ Enterobacteriaceae
↑ *Parabacteroides goldsteinii*
↓ Lactobacilli

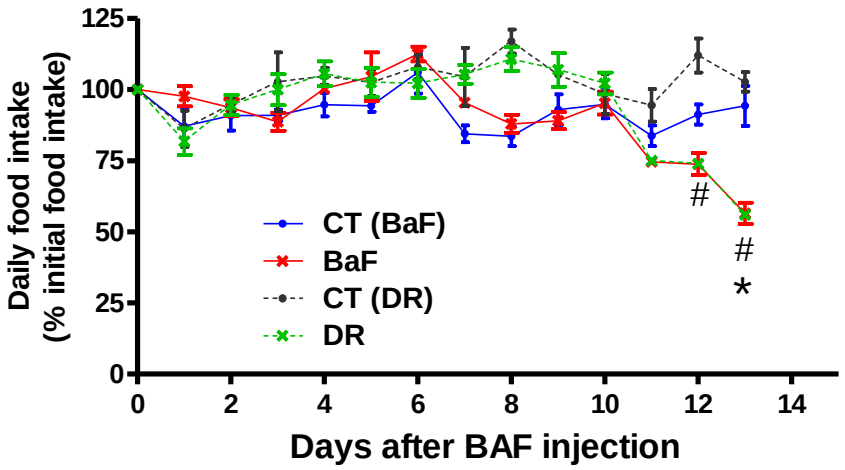
With Inès Martinez and Jens Walter

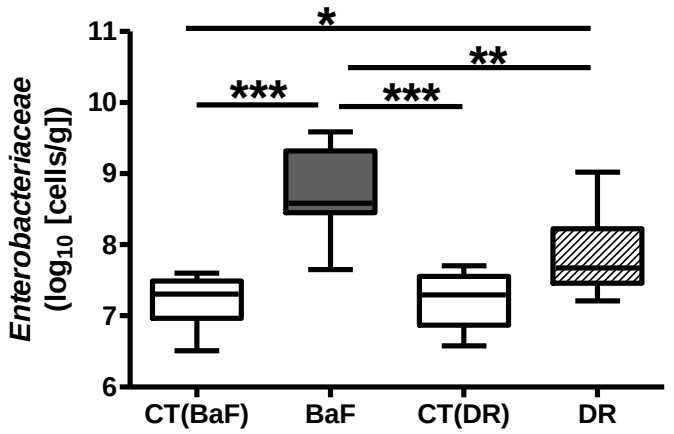
Bindels et al, The ISME J 2016

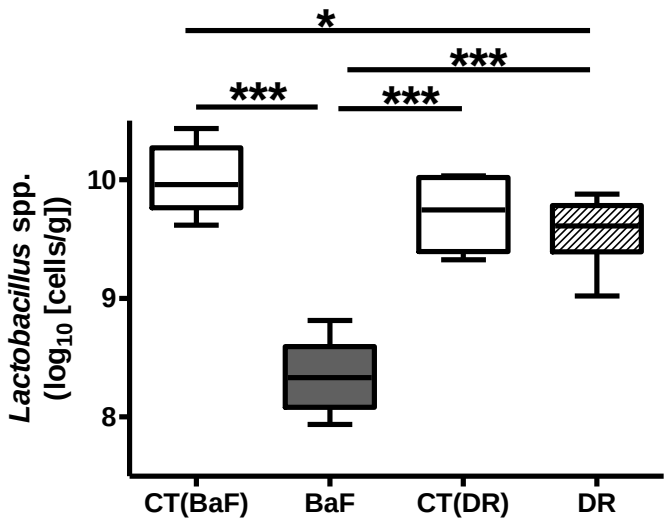
UCL Université catholique de Louvain

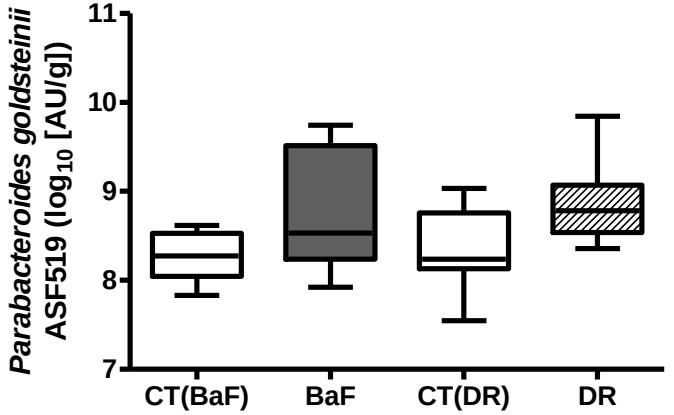
LDRI Louvain Drug Research Institute

… independent of the food intake

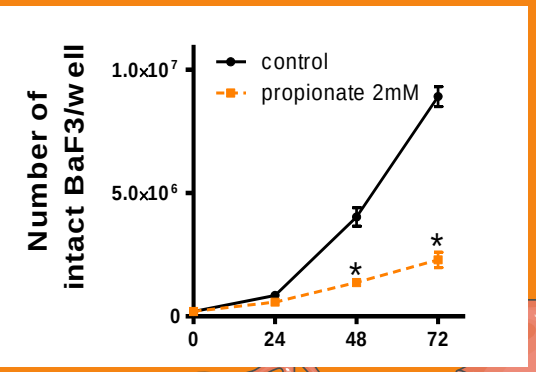


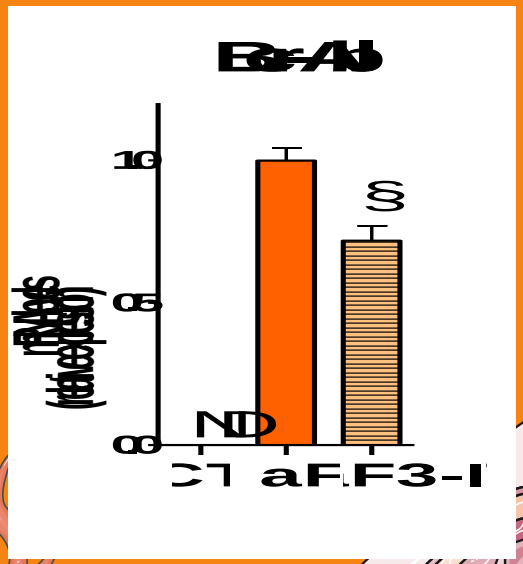




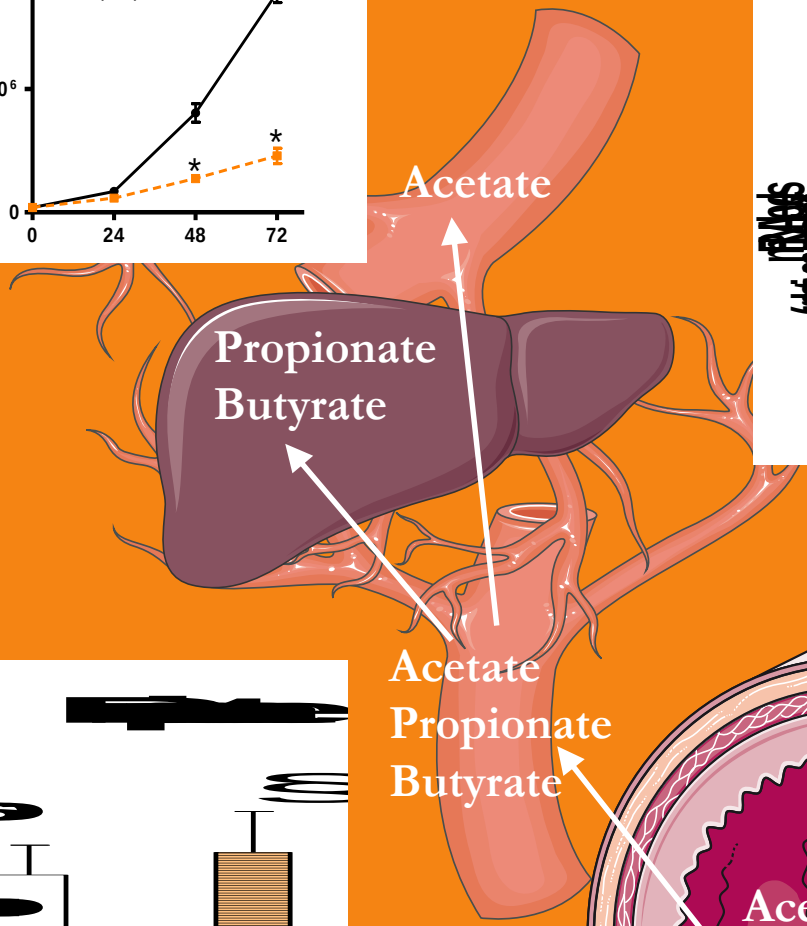


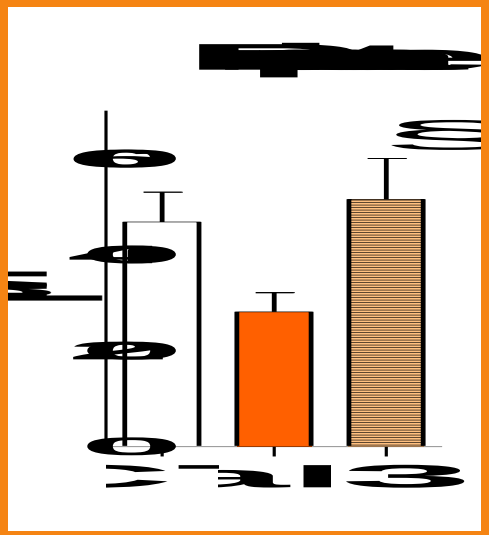
Bindels et al, The ISME J 2016

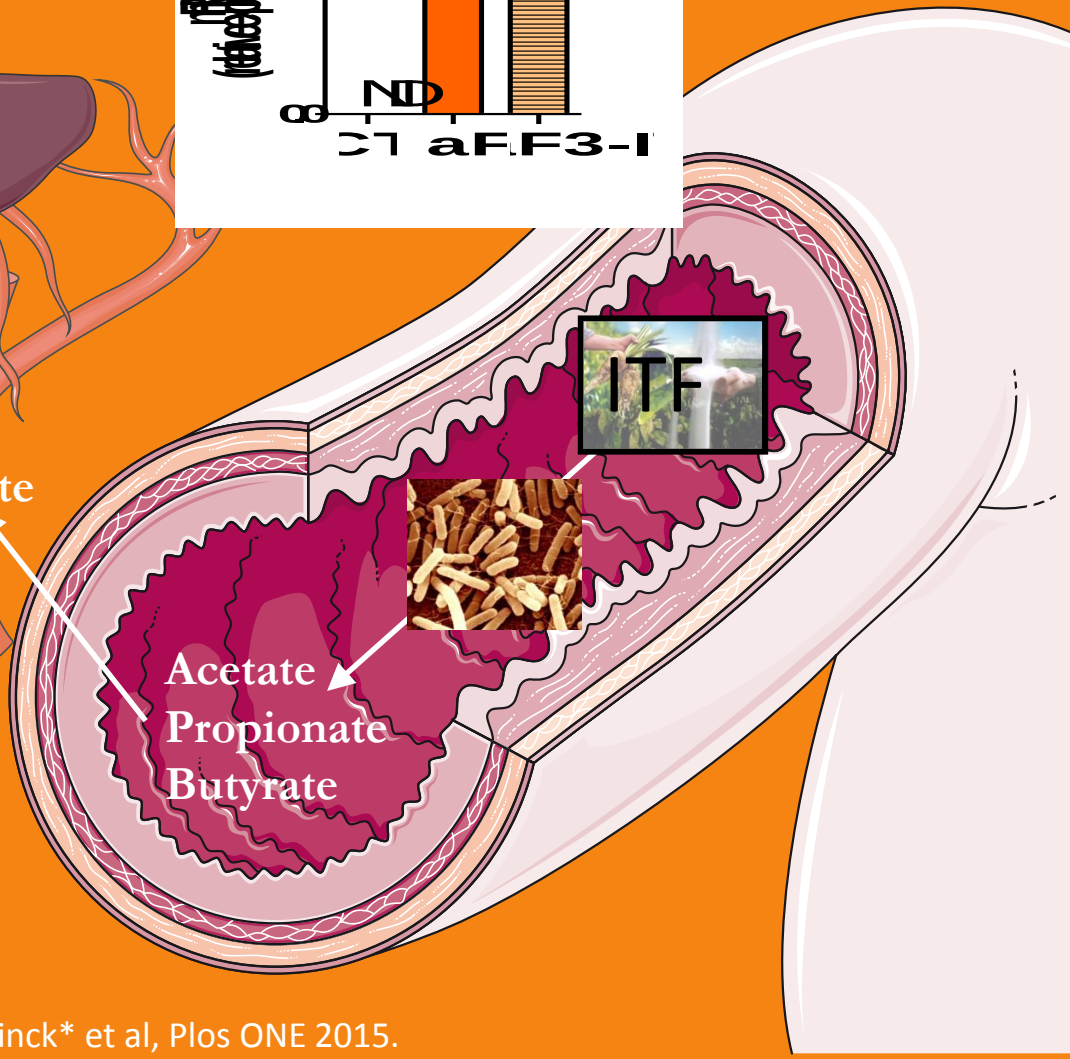




BaF

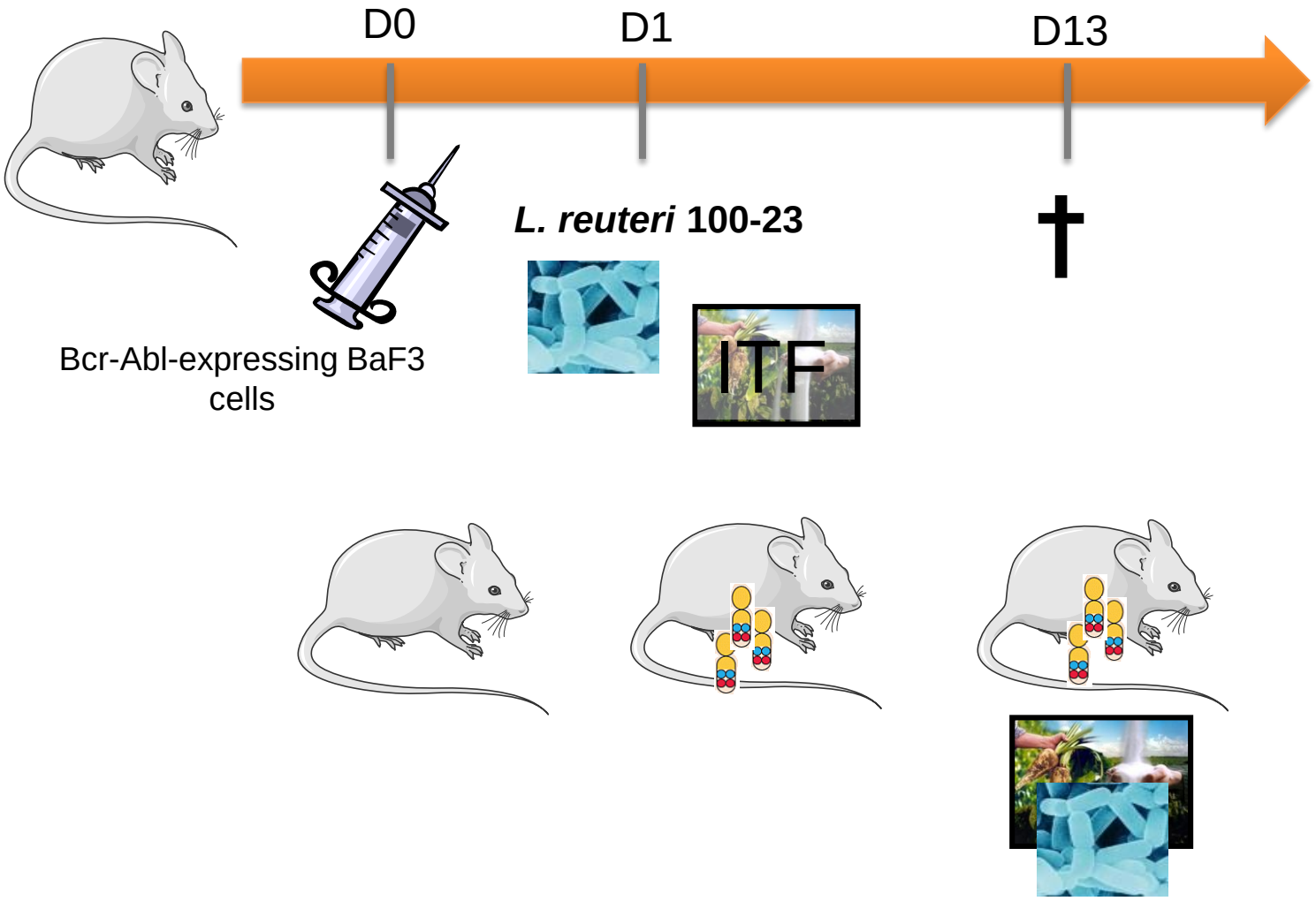






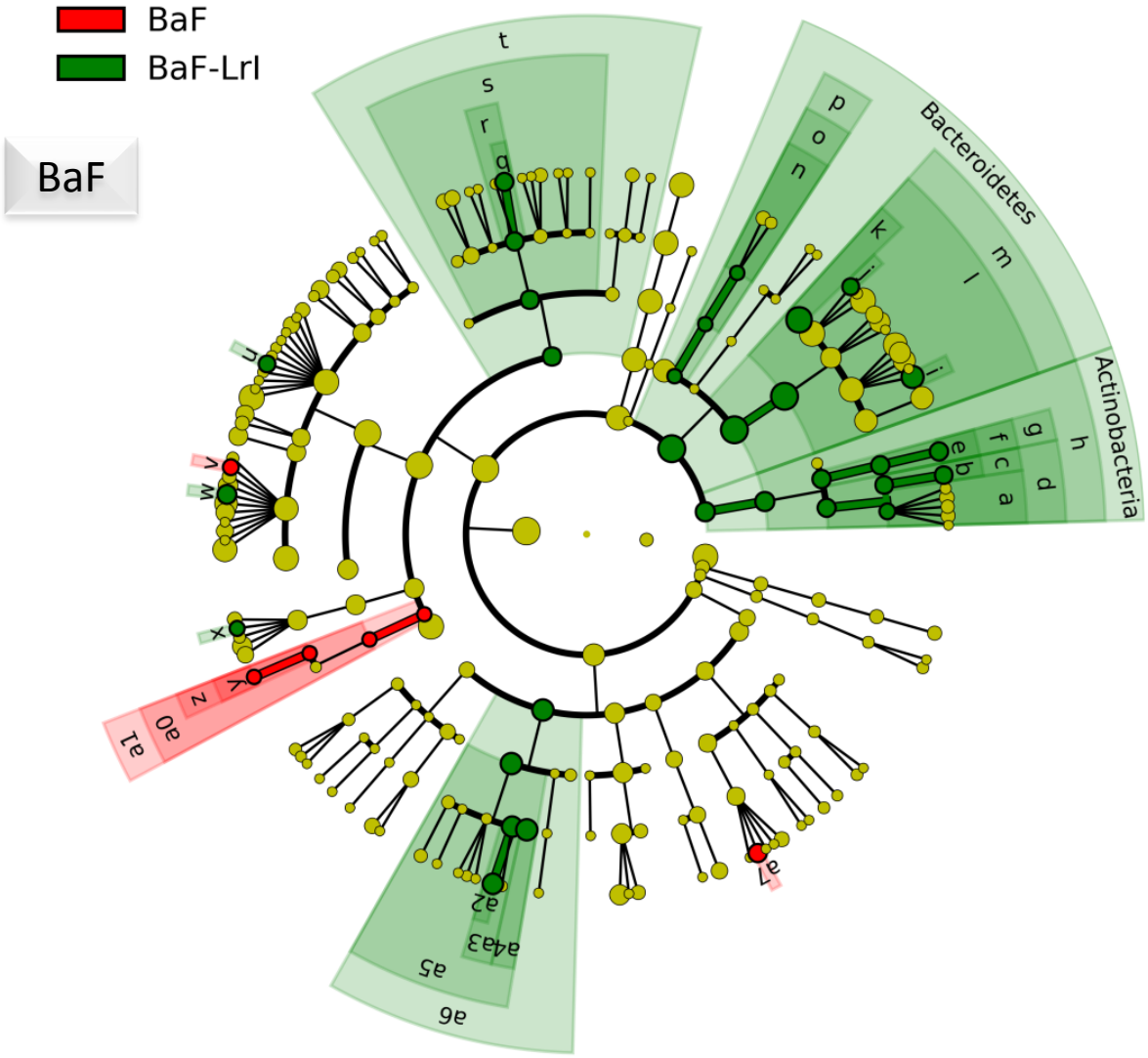
Bindels et al, Br J Cancer 2012; Bindels*, Neyrinck* et al, Plos ONE 2015.

Selected synbiotic approach



Bindels et al, The ISME J 2016

With Bruno Pot & Corinne Grangette

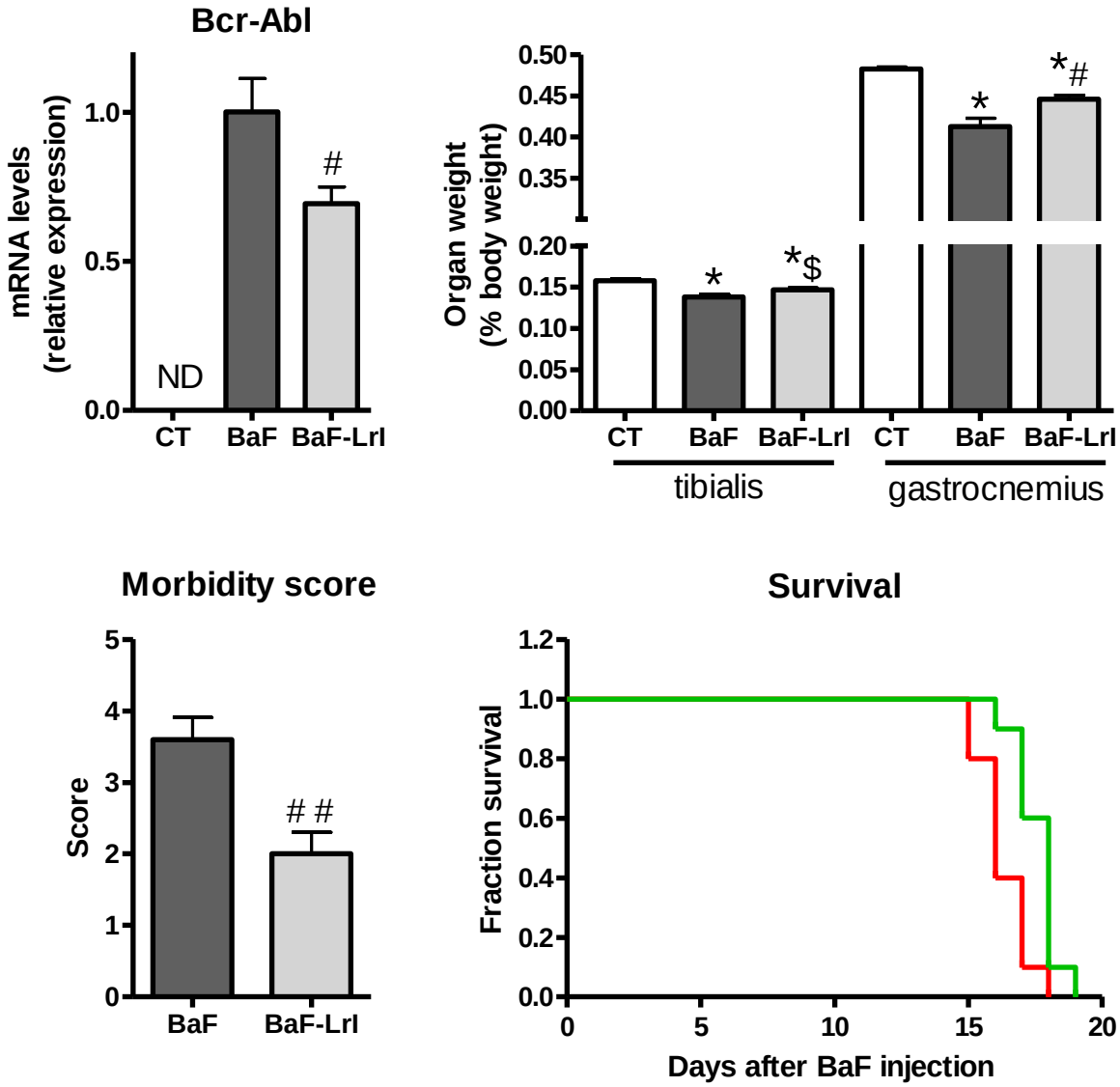


a: Actinomycetales
b: Bifidobacteriaceae
c: Bifidobacteriales
d: Actinobacteridae
e: Coriobacterineae
f: Coriobacteriales
g: Coriobacteridae
h: Actinobacteria
i: Barnesiella
j: unclassified_Rikenellaceae
k: unclassified_Bacteroidales
l: Bacteroidales
m: Bacteroidia
n: Chitinophagaceae
o: Sphingobacteriales
p: Sphingobacteria
q: Lactobacillus
r: Lactobacillaceae
s: Lactobacillales
t: Bacilli
u: Marvinbryantia
v: Anaerotruncus
w: Flavonifractor
x: ClostridiumXVIII
y: unclassified_Veillonellaceae
z: Veillonellaceae
a0: Selenomonadales
a1: Negativicutes
a2: Parasutterella
a3: Sutterellaceae
a4: unclassified_Burkholderiales
a5: Burkholderiales
a6: Betaproteobacteria
a7: Escherichia_Shigella

16S rRNA genes from the caecal microbiota analysed by Illumina MiSeq. LEfSe cladogram.

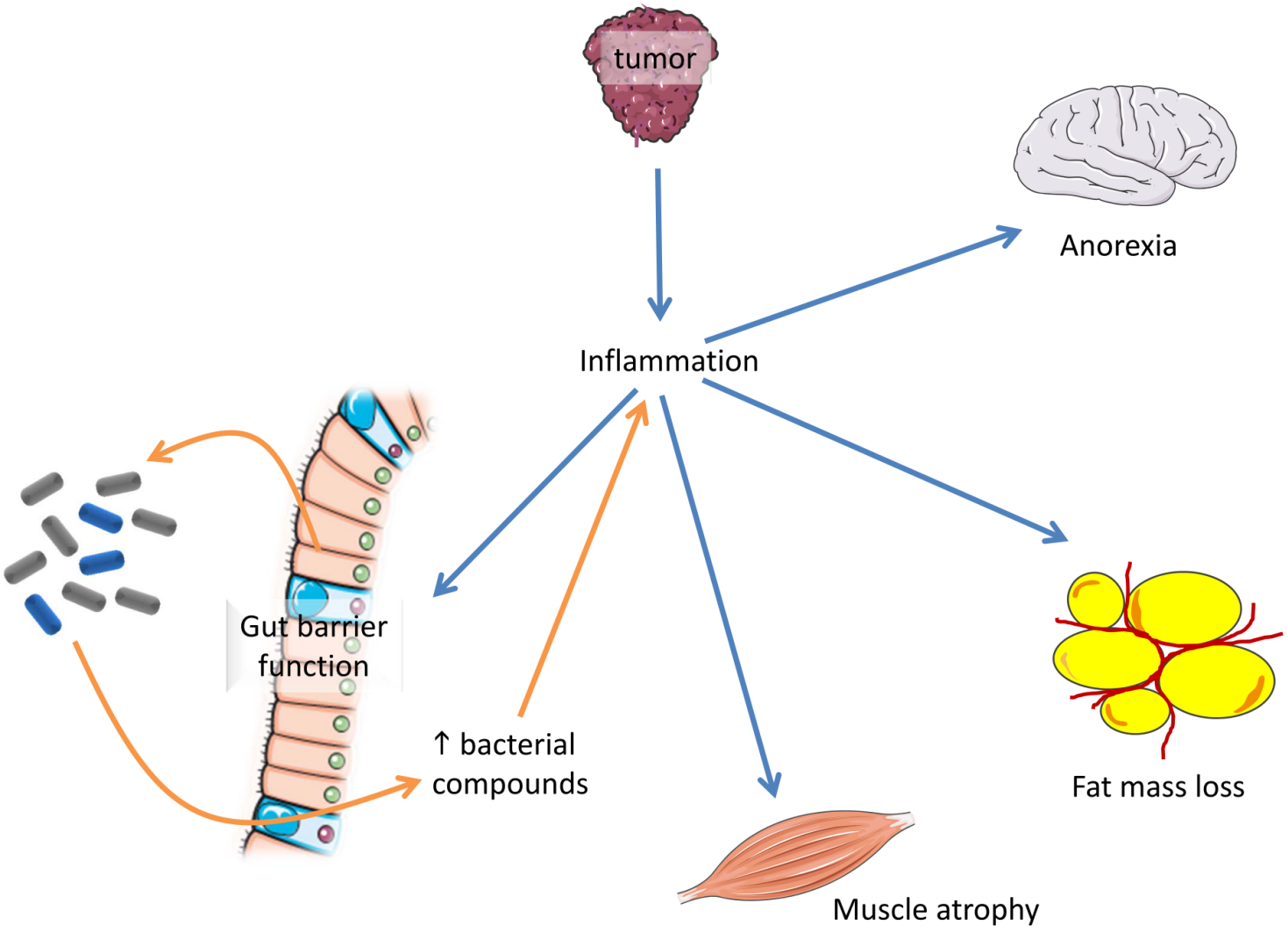
Benefits of the synbiotic approach

BaF



Bindels et al, The ISME J 2016

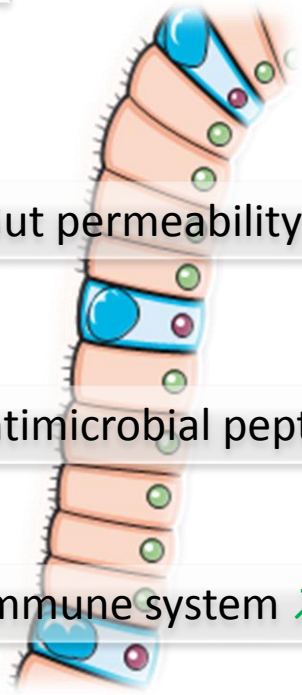
Hypothetical role of the gut barrier



Bindels & Thissen, Clin Nutr Exp 2015

Hypothetical role of the gut barrier

BaF



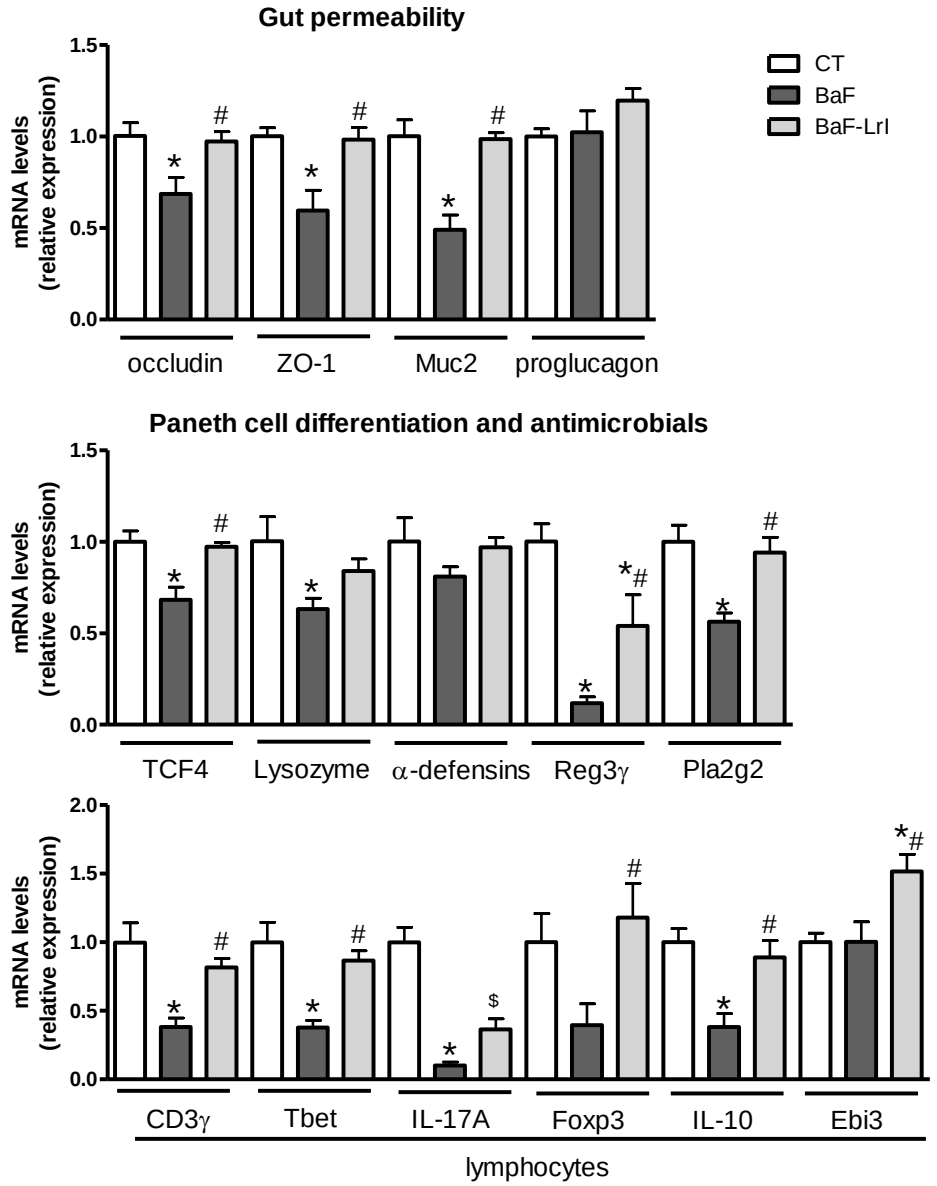
↘ Gut permeability ↗

↘ Antimicrobial peptides ↗

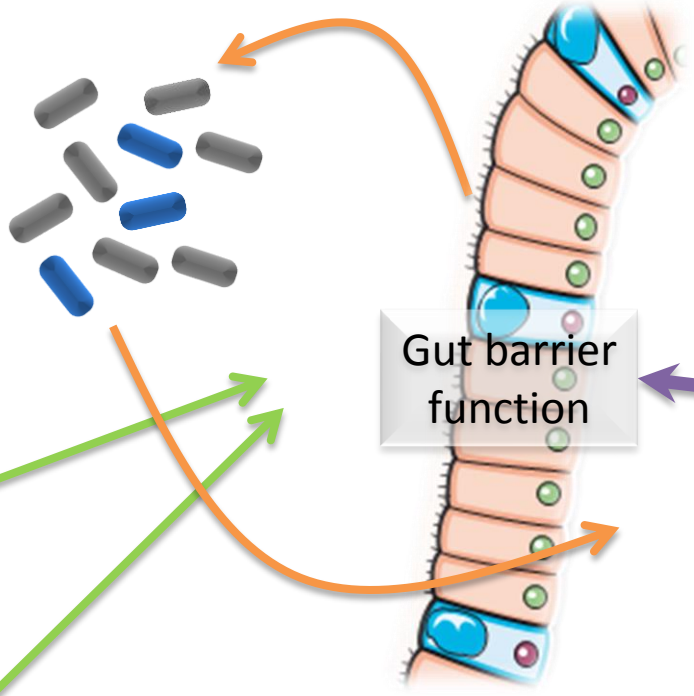
↘ Immune system ↗

↘ Decreased in leukemic mice

↗ Increased by synbiotics



Current working model



Gut barrier function

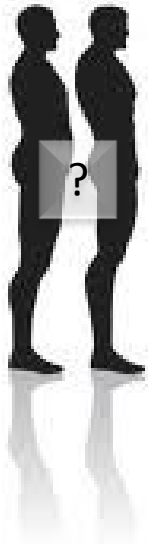
Cancer cachexia

Probiotics

Prebiotics

Propionate

New metabolites ?



?

Outline

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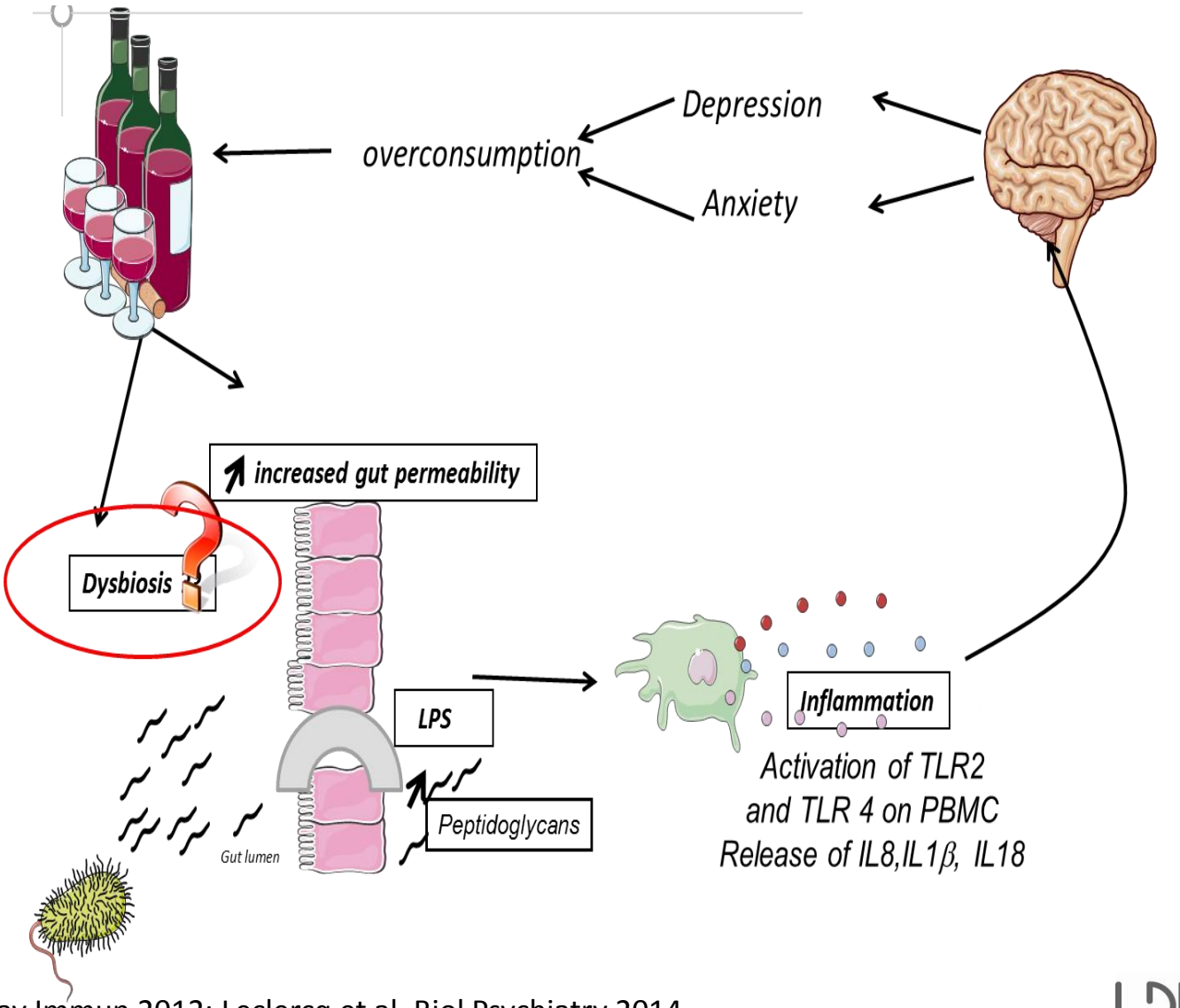
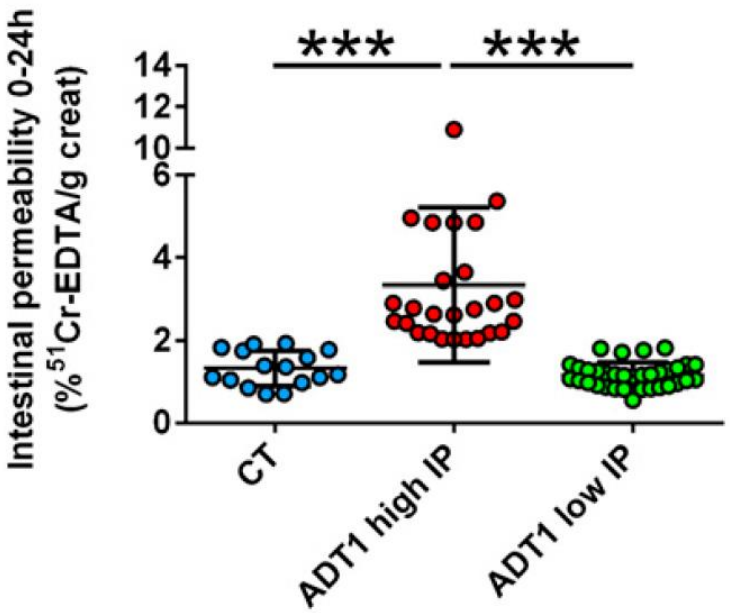
4. **Gut microbiota in alcohol-dependent patients**

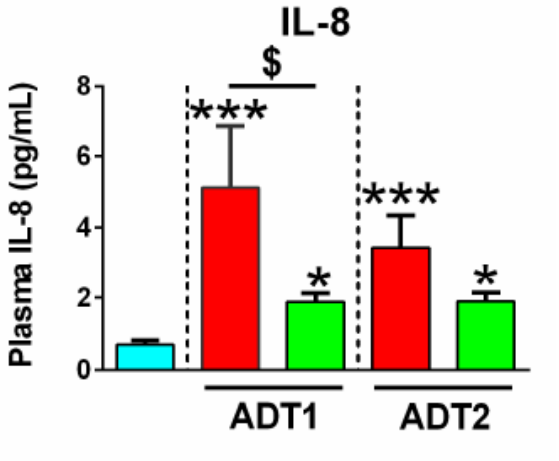
A role for the gut permeability?

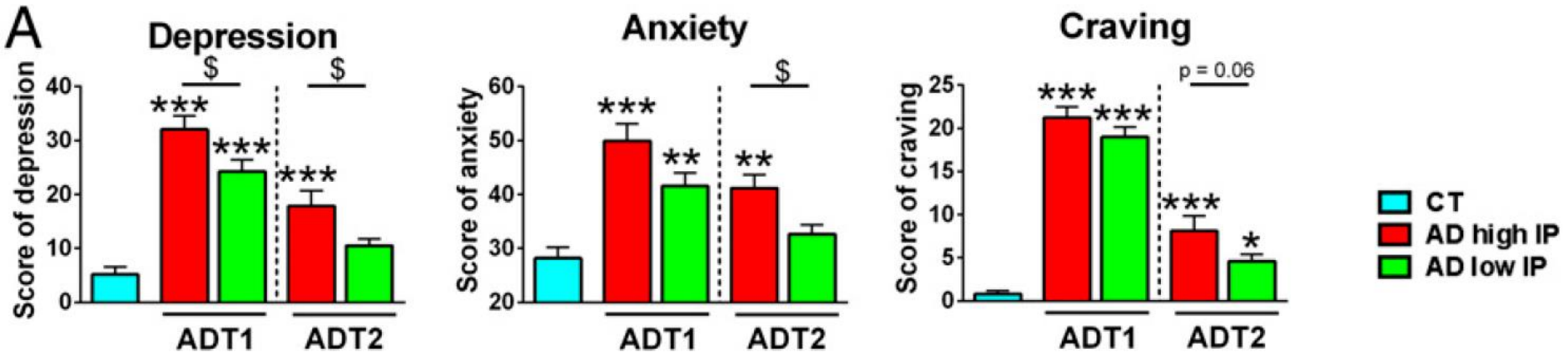


Leclercq et al, Brain Behav Immun 2012; Leclercq et al, Biol Psychiatry 2014.

A role for the gut permeability ?

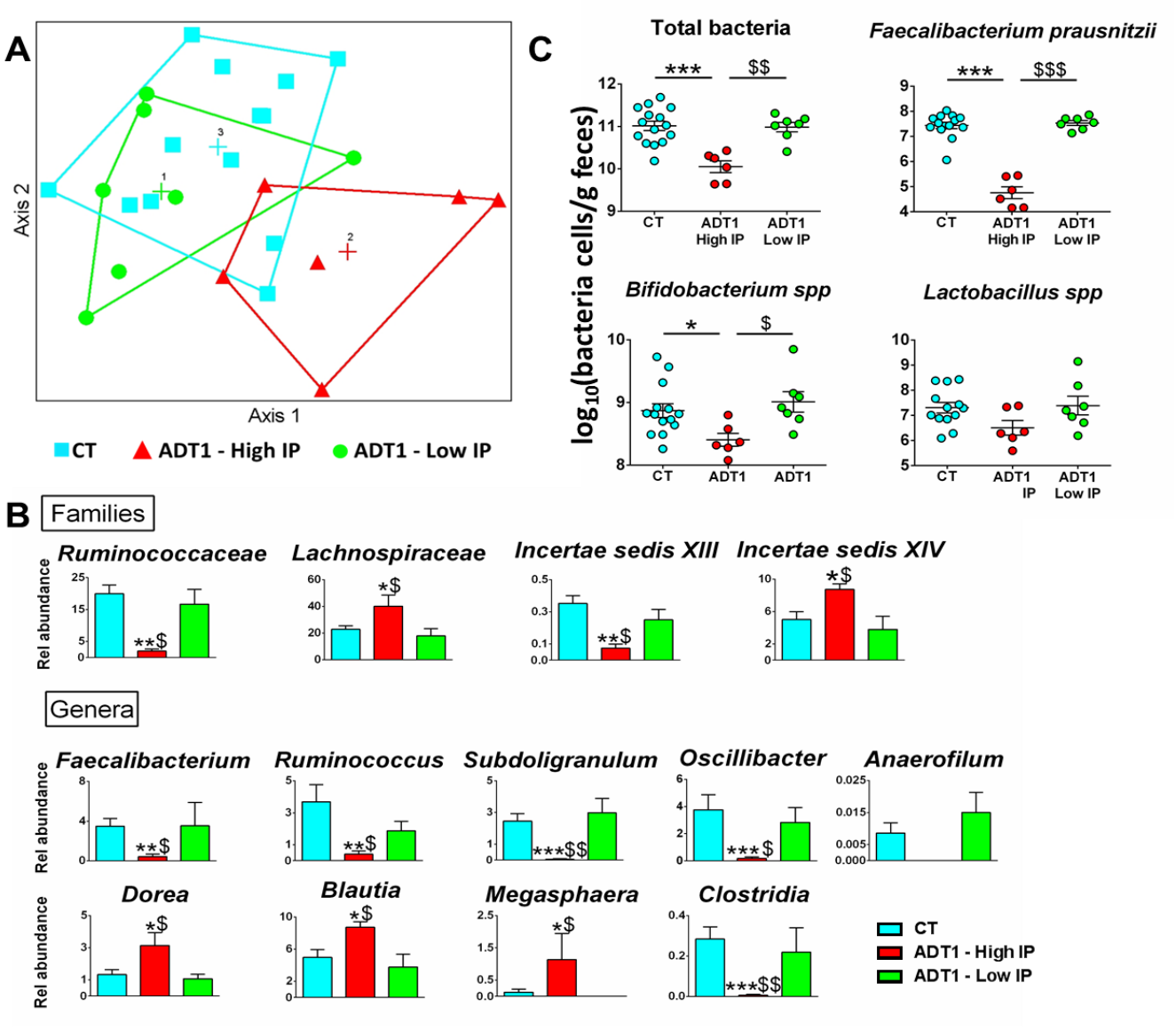






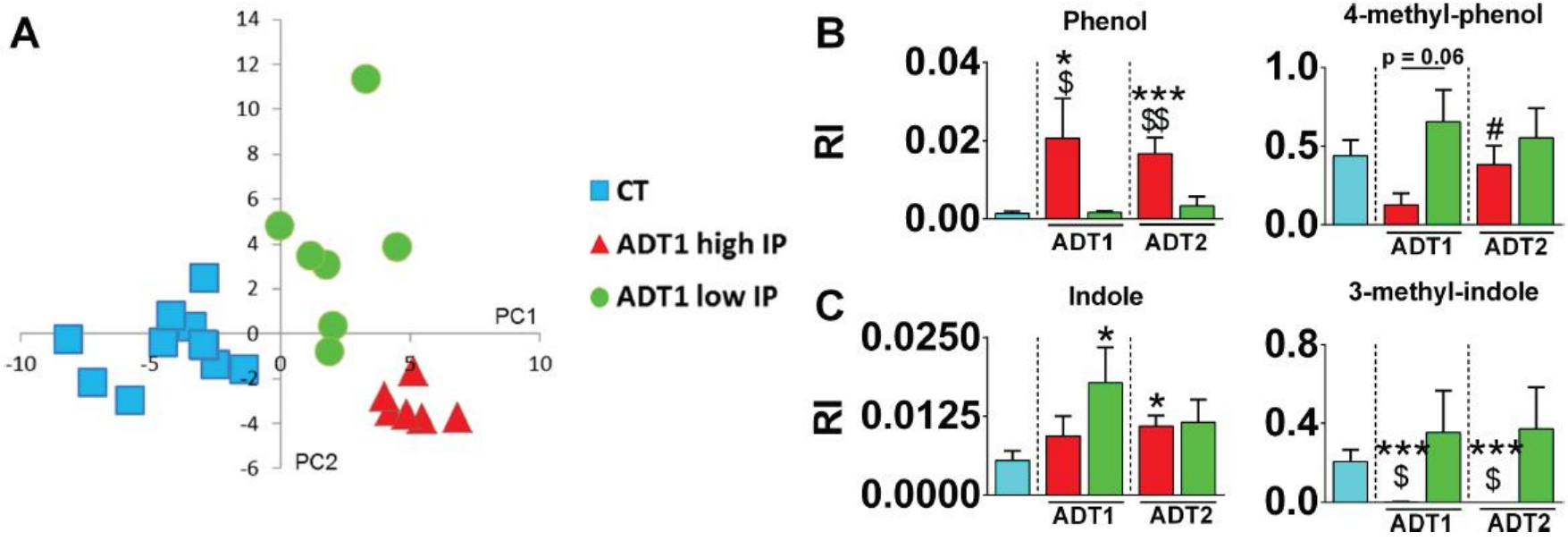
Leclercq et al, PNAS 2014

Dysbiosis



Leclercq et al, PNAS 2014

Altered fecal metabolite profil



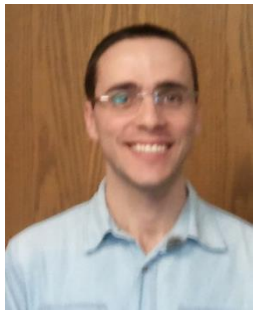
Analysis of Volatile organic compounds by gas-chromatography-mass spectrometry (K. Verbeke, Kuleuven B)
Bi-plot analysis reveals ADT1 HP- versus LP are differentiated (14 metabolites)

Conclusions

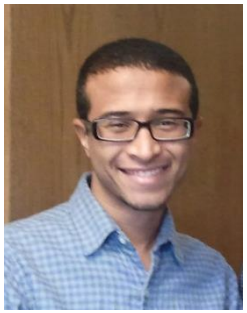
- Importance of the prebiotic concept.
- Microbiota-dependent and independent effects of functional foods: strategies to demonstrate causality exist.
- Underexplored areas could benefit from targeted prebiotic or synbiotic approaches.

University of Nebraska Lincoln

Prof. Amanda Ramer-Tait



Carlos Gomes Neto



Hatem Kittana

Rafael Segura Munoz

UNL Gnotobiotic Mouse Facility
Robert Schmaltz
Brandon White

Prof. Jens Walter

Liz Cody

Dr. Inés Martínez

UCL Université catholique de Louvain

FSR Fellowship

GUT function initiative

Maria Isabel Quintero
Junyi Yang
Maria Ximena Maldonado-Gomez

ESPEN

UCL Université catholique de Louvain

LDRI LOUVAIN DRUG RESEARCH INSTITUTE

fnrs LA LIBERTÉ DE CHERCHER

Wallonie

Post-doc position in July 2017 : laure.bindels@uclouvain.be

UCL (BE)
Prof G. Muccioli
Prof P. Buc Calderon
Prof J.P. Thissen
Prof O. Feron
Prof P. Sonveaux
Dr P. Porporato
Dr J. Verrax
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