Better Food for Better Health
Microbiota and Health : the challenges of a promising approach

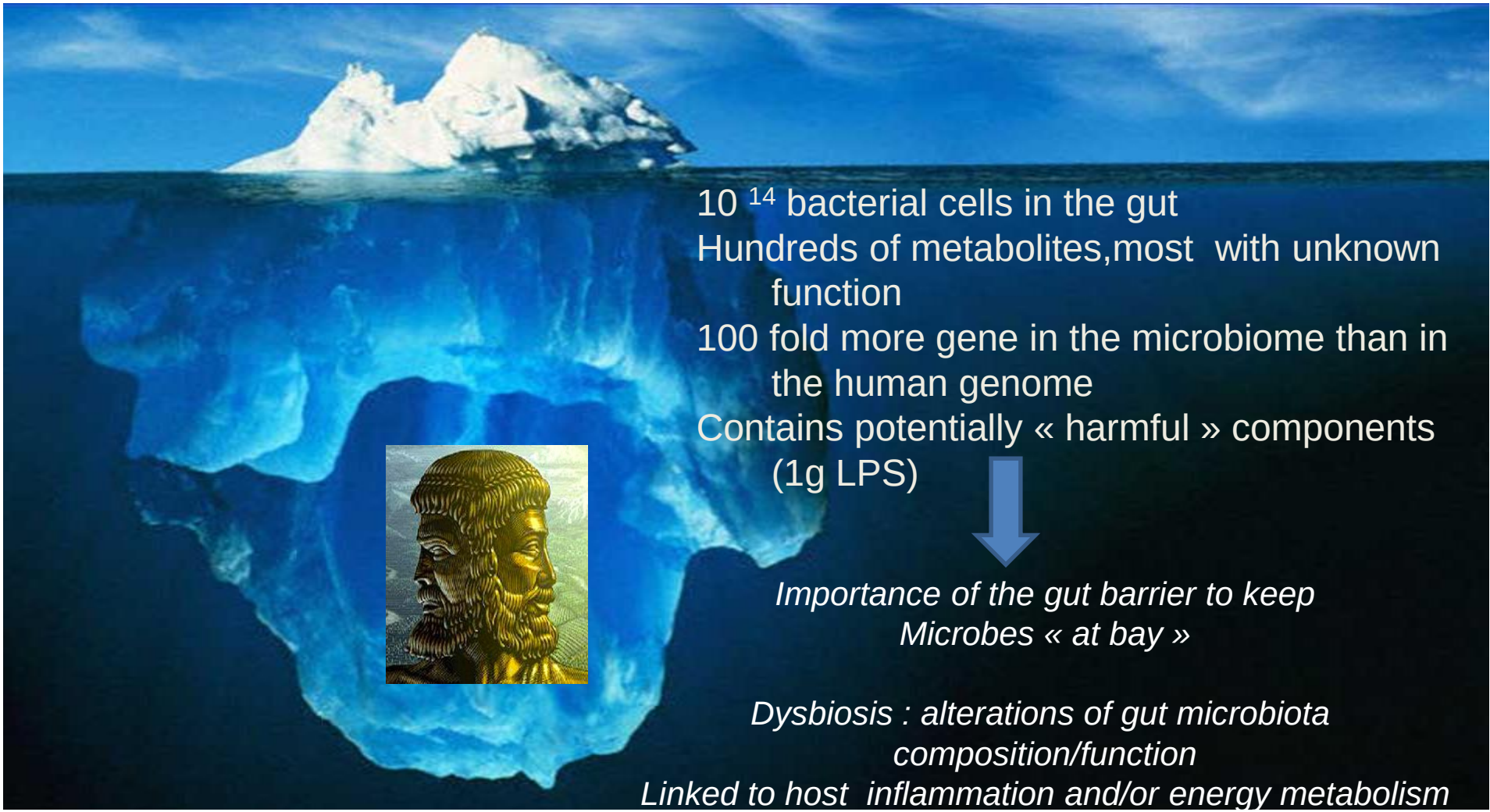
Fondation Mérieux, Veyrier du Lac, France
6-8th april 2016

Treatment options : pre and probiotics for treatment of malnutrition and cachexia

Nathalie Delzenne, Laure Bindels

I declare no conflict of interest related to this presentation

The Gut Microbiota: an internal organ we feed everyday



10 ^{14} bacterial cells in the gut

Hundreds of metabolites,most with unknown function

100 fold more gene in the microbiome than in the human genome

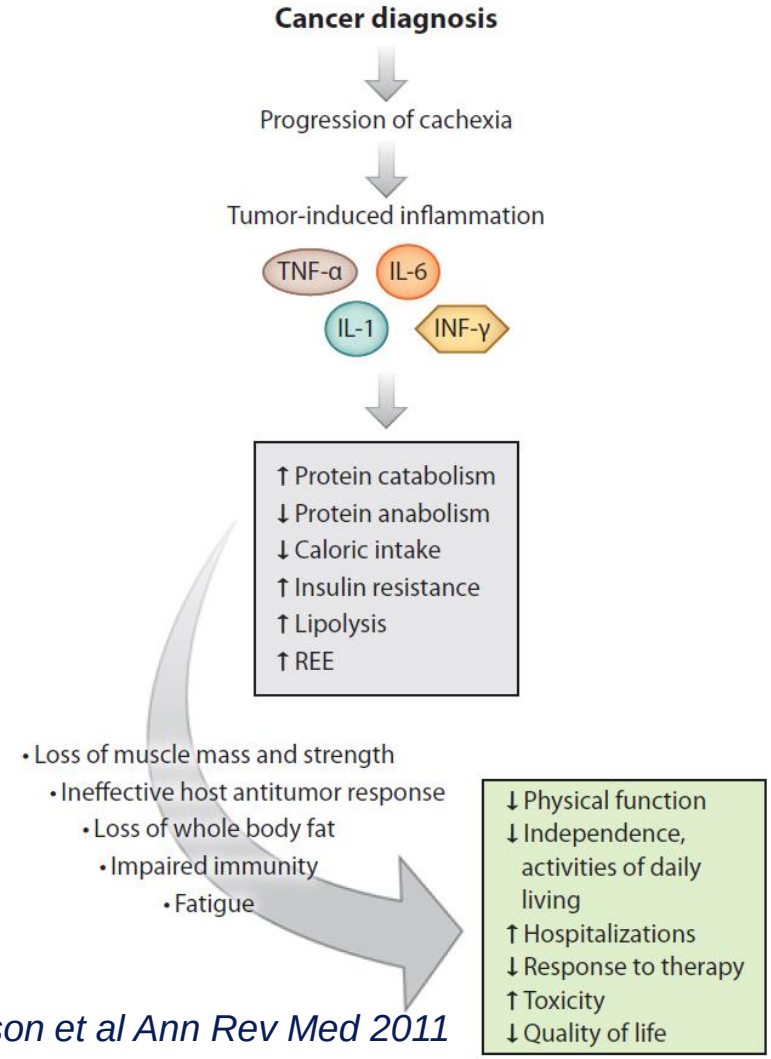
Contains potentially « harmful » components (1g LPS)

Importance of the gut barrier to keep Microbes « at bay »

Dysbiosis : alterations of gut microbiota composition/function

Linked to host inflammation and/or energy metabolism

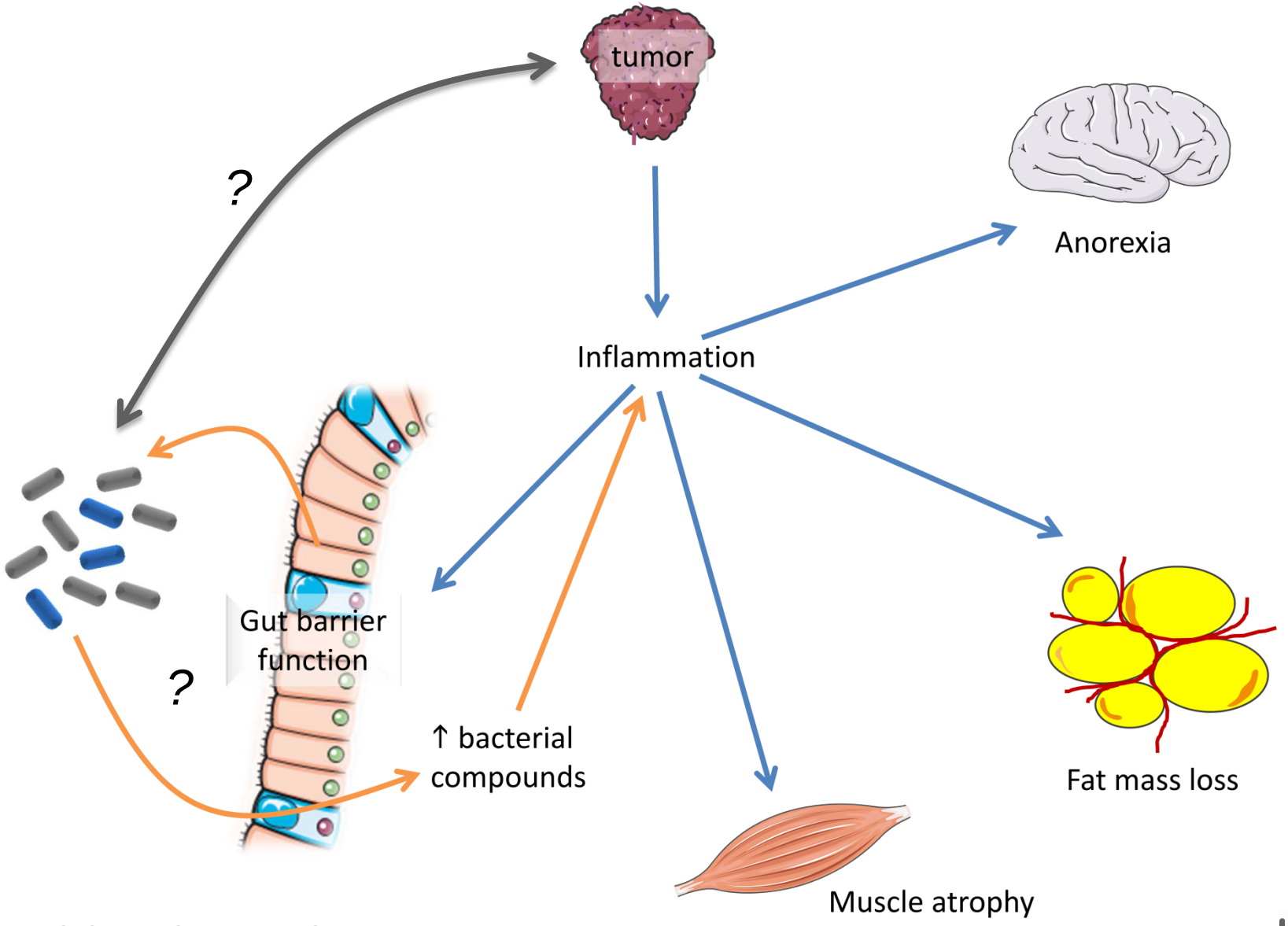
A role for gut microbiota in cancer-related malnutrition ?



Dadson et al Ann Rev Med 2011

- Cancer cachexia : loss of muscle and fat mass, with consequence on lifespan and quality of life.
- Not only due to radio-chimio-therapy, or appetite loss; also linked to inflammation.
- Frequent ; 50- 80 % cancer patients; associated with colon cancer and acute non-lymphocytic leukemia and chronic myeloid leukemia

A link between gut microbial dysbiosis and cancer cachexia ?

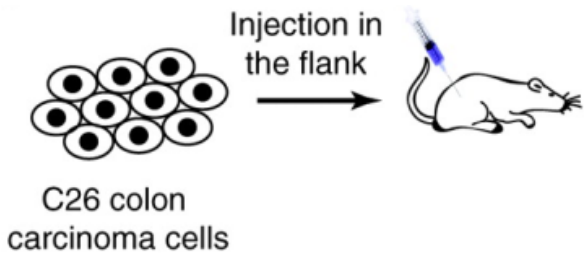


Bindels & Thissen, Clin Nutr Exp, *in press*

Link between gut microbiota in cancer cachexia
Experimental approach

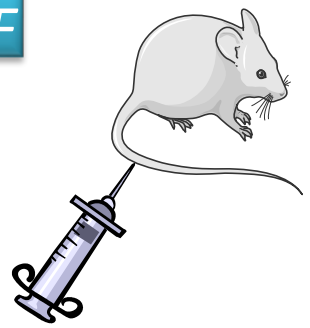
- Community-wide approach to characterize the gut microbiota in two mouse models of cancer cachexia (ectopic tumor transplantation)
- Rapid tumor development, linking to weight loss, with critical outcome from day 12-13

C26



Local development of tumor associated with cachexia

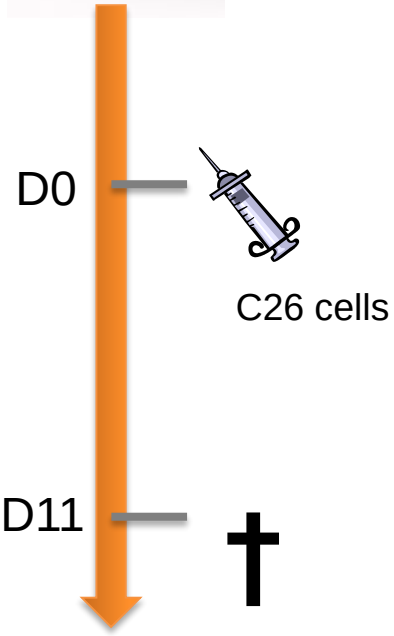
BAF

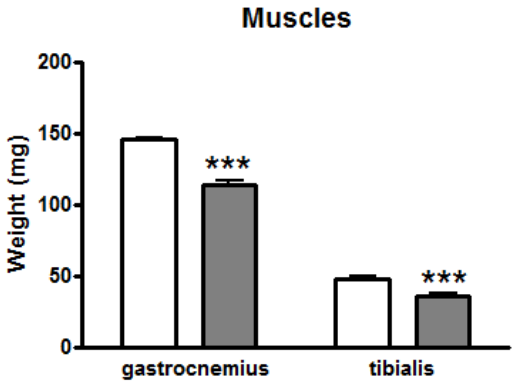


BaF3 cells with Bcr-Abl

Mimics leukemia
Accumulation of tumor cells in the spleen and liver

Cancer cachexia C26 model





Bindels et al., The ISME J, 12/2015

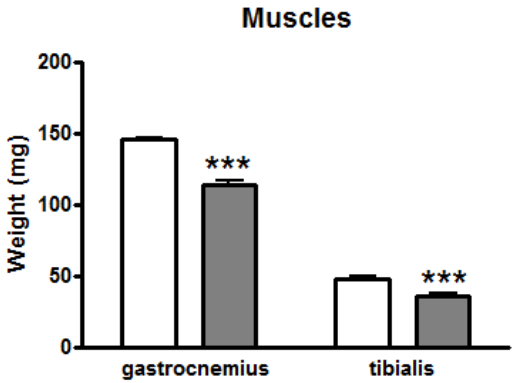
Cancer cachexia C26 model

D0

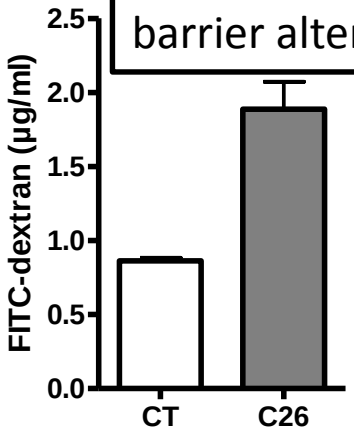
C26 cells

D11

†

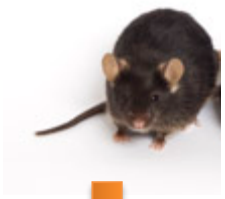


PLASMA dextran FITC after gavage : gut barrier alterations



Bindels et al ISME J. 2015

Cancer cachexia C26 model



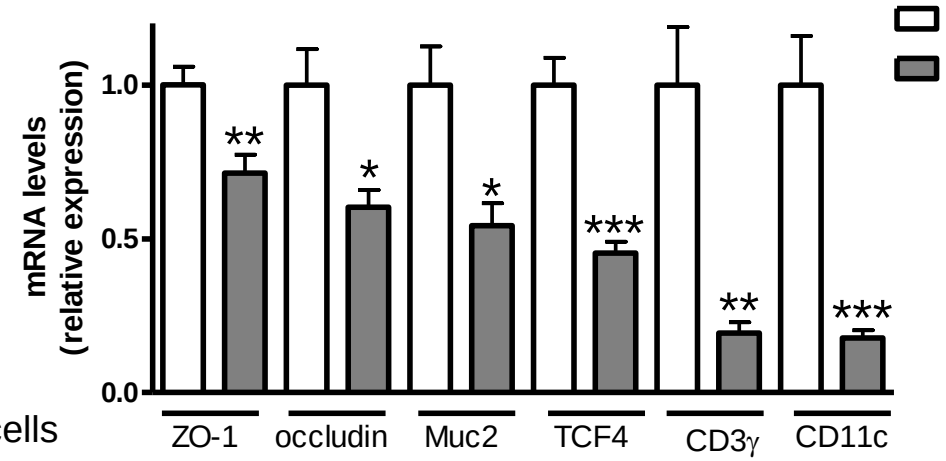
D0

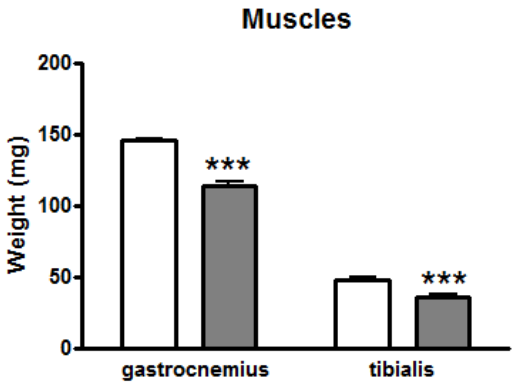
C26 cells

D11

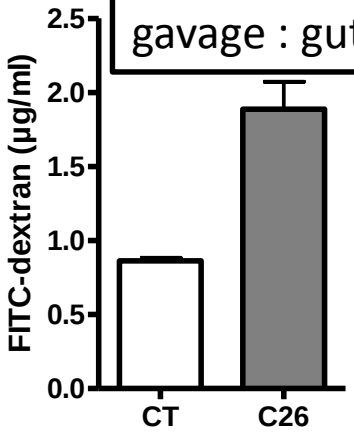
†

SMALL INTESTINE : gut function and immunity





PLASMA dextran FITC after gavage : gut permeability



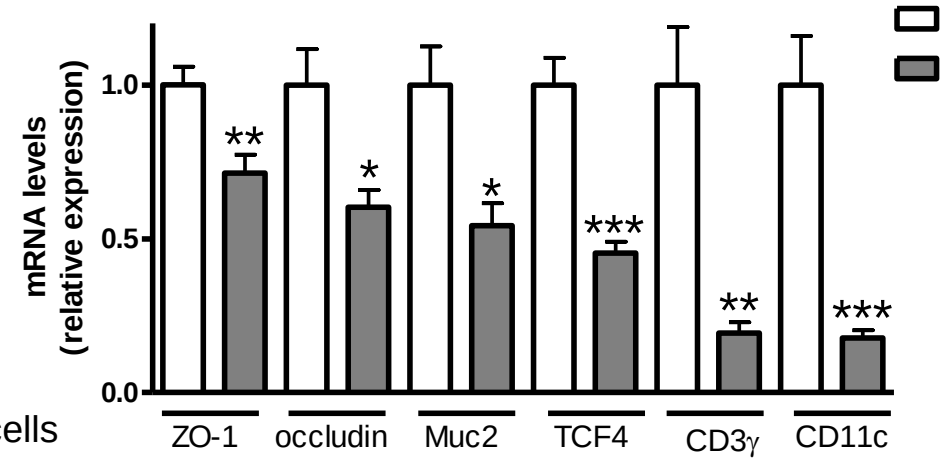
Cancer cachexia C26 model

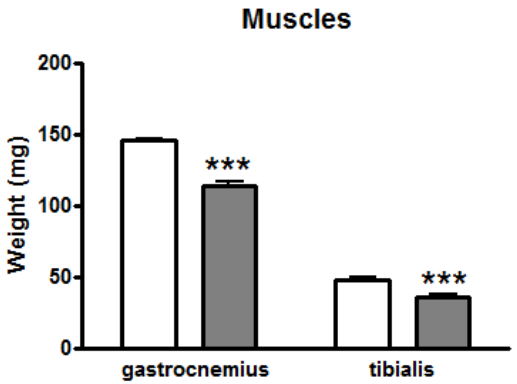
D0

C26 cells

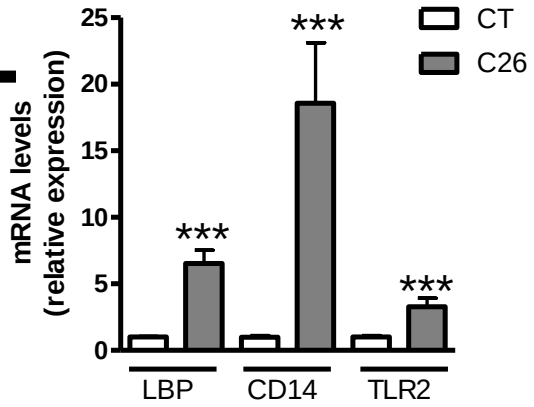
D11

SMALL INTESTINE

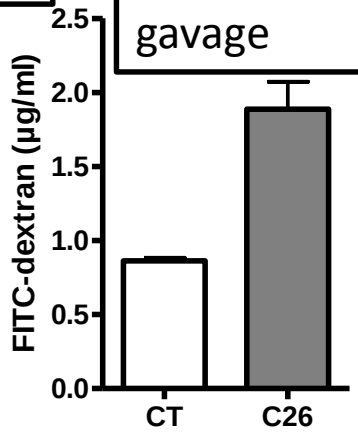




LIVER : (LPS) inflammation



PLASMA dextran FITC after gavage



Changes in gut microbiota?

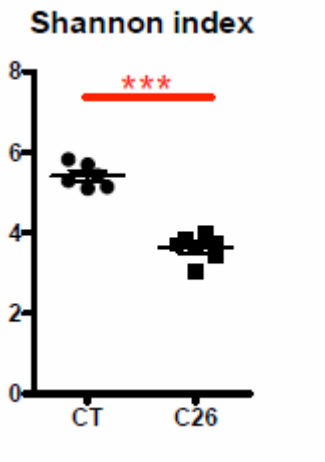
Dysbiosis in cancer cachexia

D0

C26 cells

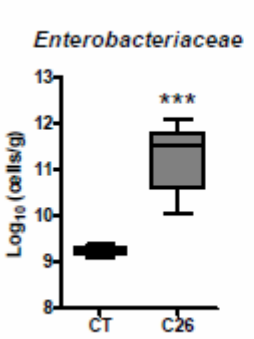
D11

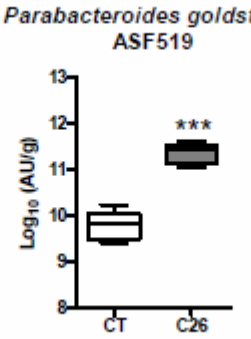
†

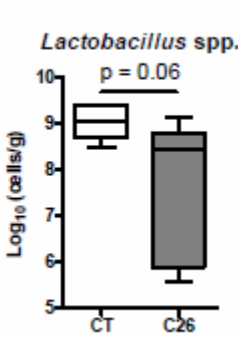


Decreased diversity

H

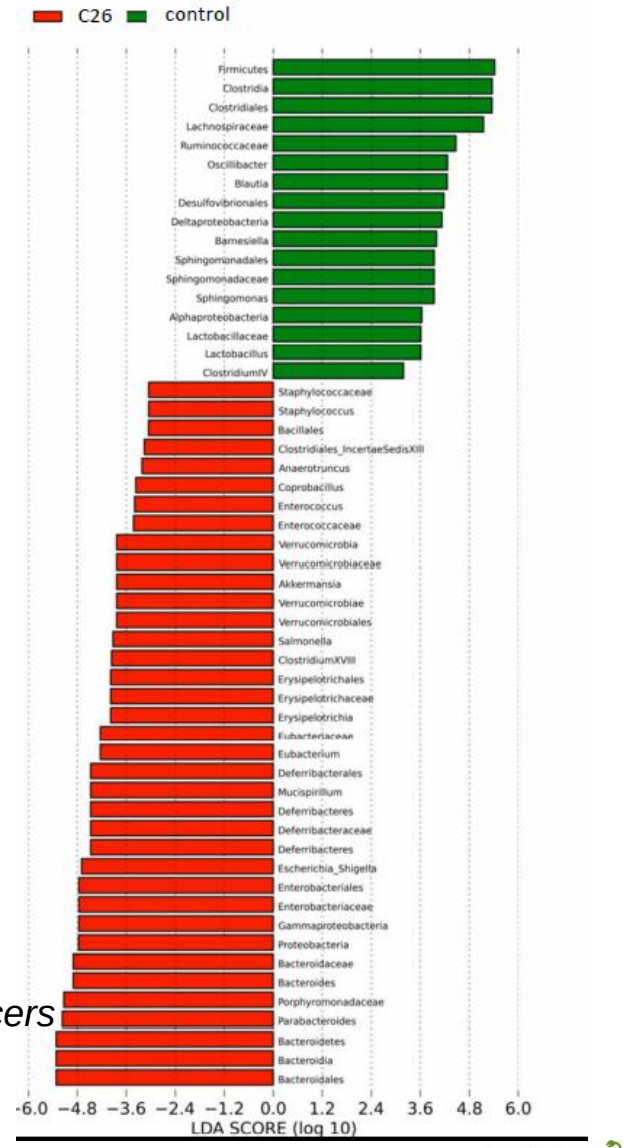






Increased « pathobionts »

Increased Lactic acid producers

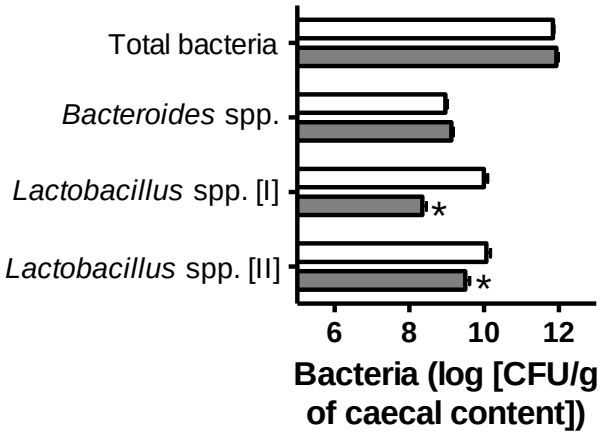


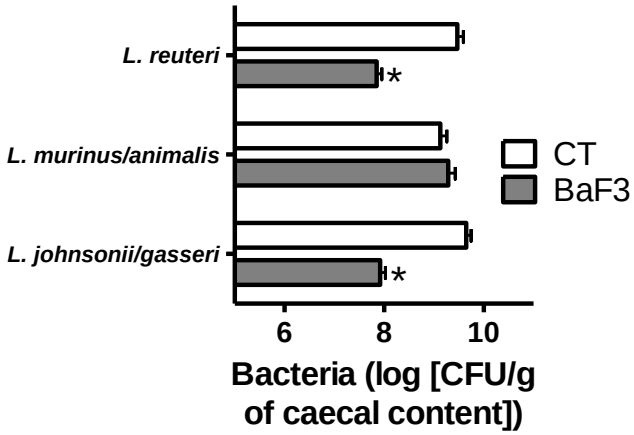
Bindels et al, Isme J 2015

UCL Université catholique de Louvain

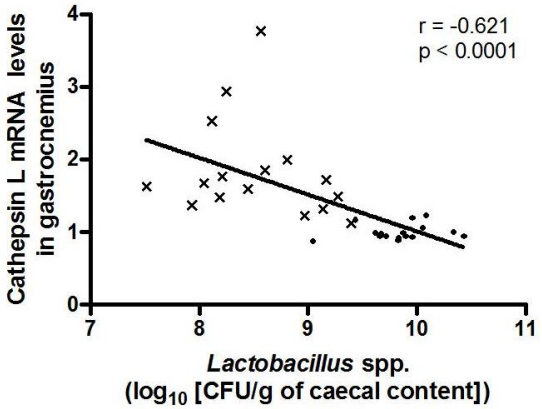
LDRI Louvain Drug Research Institute

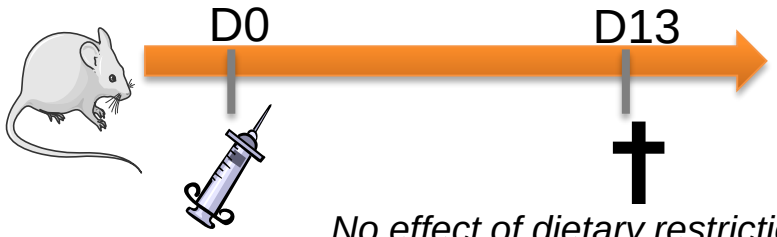
Cancer cachexia linked to leukemia model





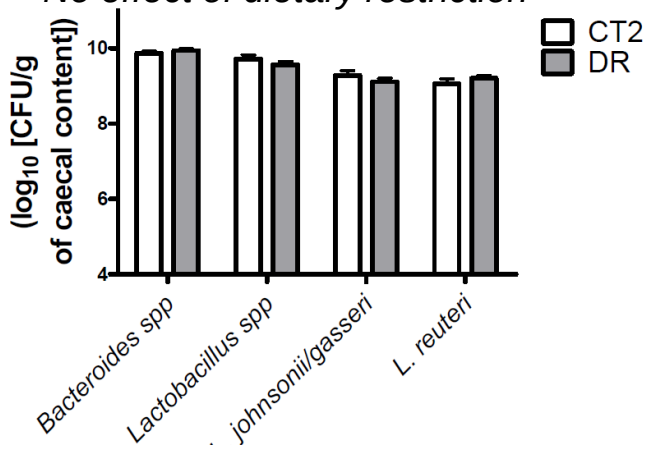
Muscle atrophia

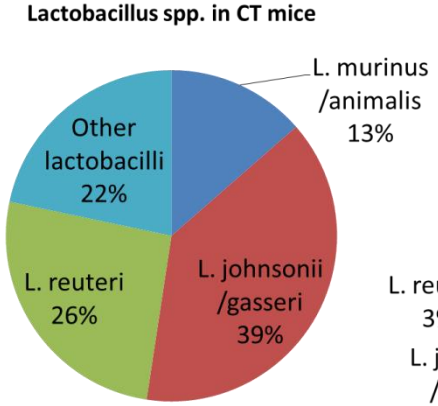


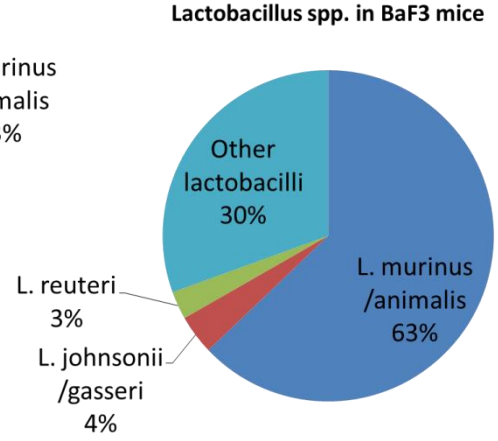


Bcr-Abl-expressing BaF3 cells

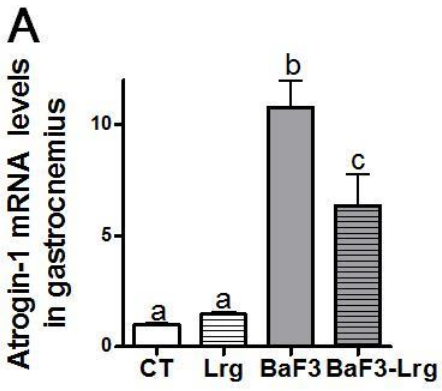
No effect of dietary restriction

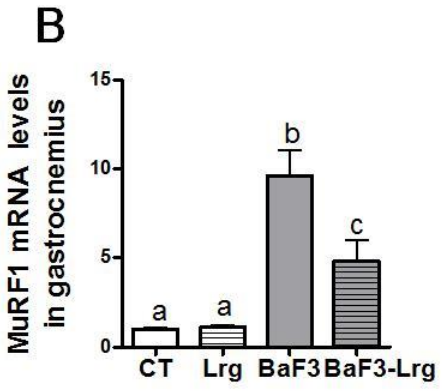


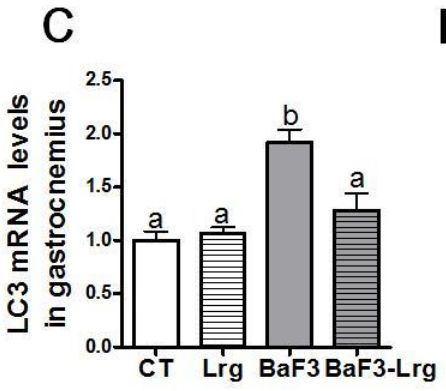


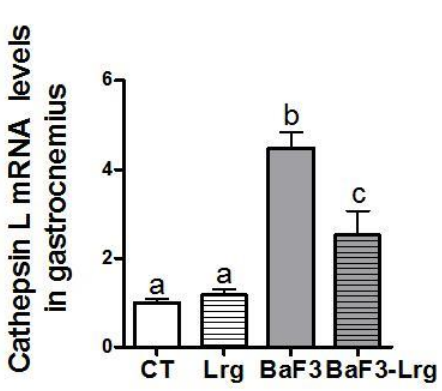


Bindels et al, Plos ONE 2012





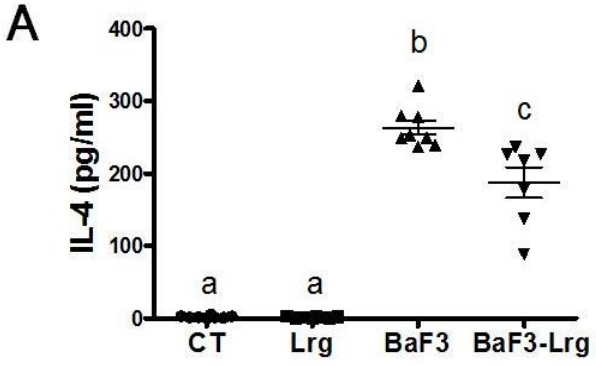


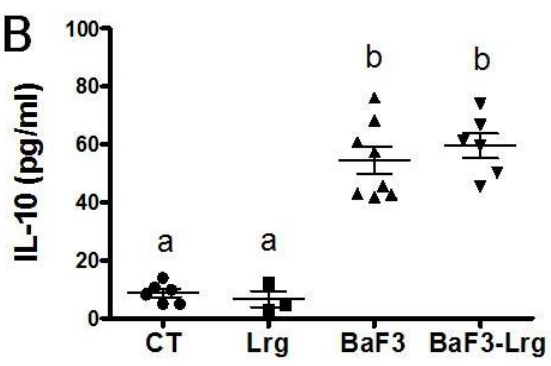


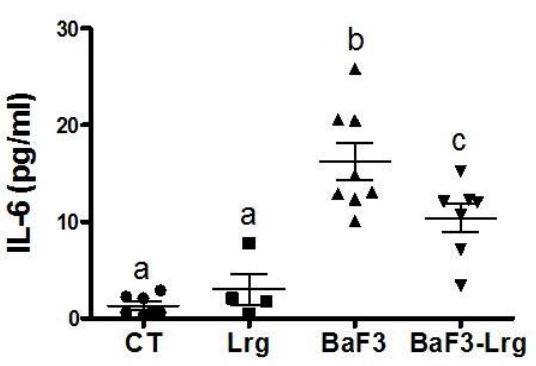
improves muscle atrophy

« Probiotic approach » Lactobacillus reuteri 100-23 + Lactobacillus gasseri 311476 5x10^8 cfu (BaF3 -Lrg group)

modulates systemic inflammation







Probiotics & Prebiotics in cancer cachexia

Probiotics: live microorganisms which, when administered in adequate amounts, confer a health benefit to the host.

i.e. *Lactobacilli*

FAO 2001; Hill et al, Nat Rev Gastroenterol Hepatol 2014

Prebiotics: non digestible compounds which stimulate the growth/activity of bacteria that confer health benefits to the host.

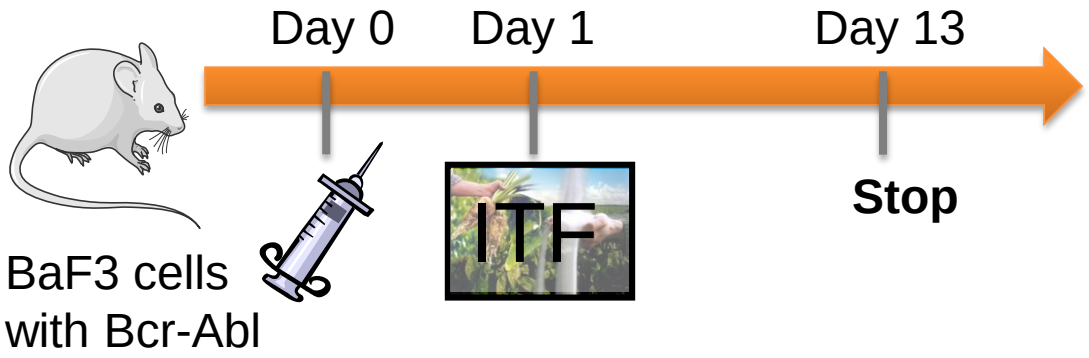
i.e. Inulin-type fructans : non digested, fermented

by bacteria expressing beta-fructosidase (Bifidobacteria) into

gaz and short chain fatty acids

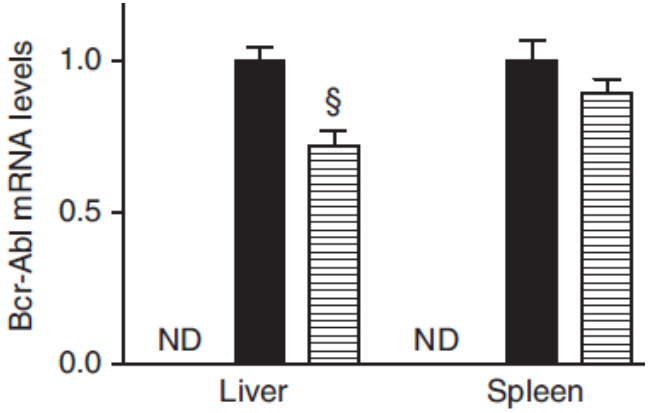
Roberfroid et al, Br J Nutr 2010; Bindels et al, Nat Rev Gastroenterol Hepatol 2015

Prebiotic approach : inulin-type fructans (ITF) added in the diet (5%)

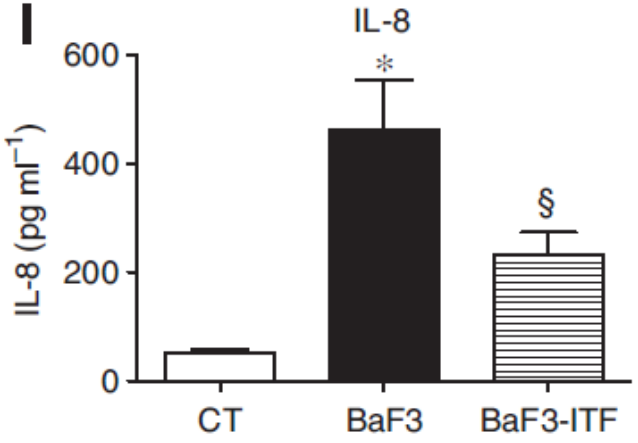


ITF has no effect on lactobacilli level, and does not change muscle atrophy but ….

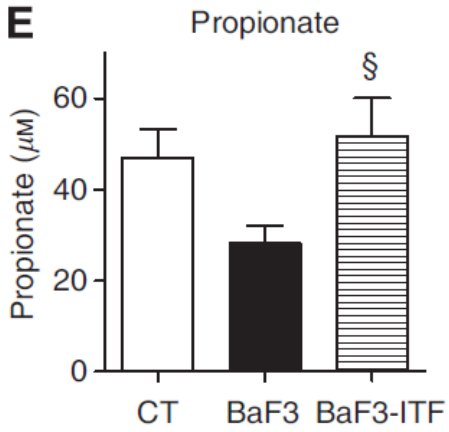
Decreases cancer cell proliferation in the liver



Decreases systemic inflammation



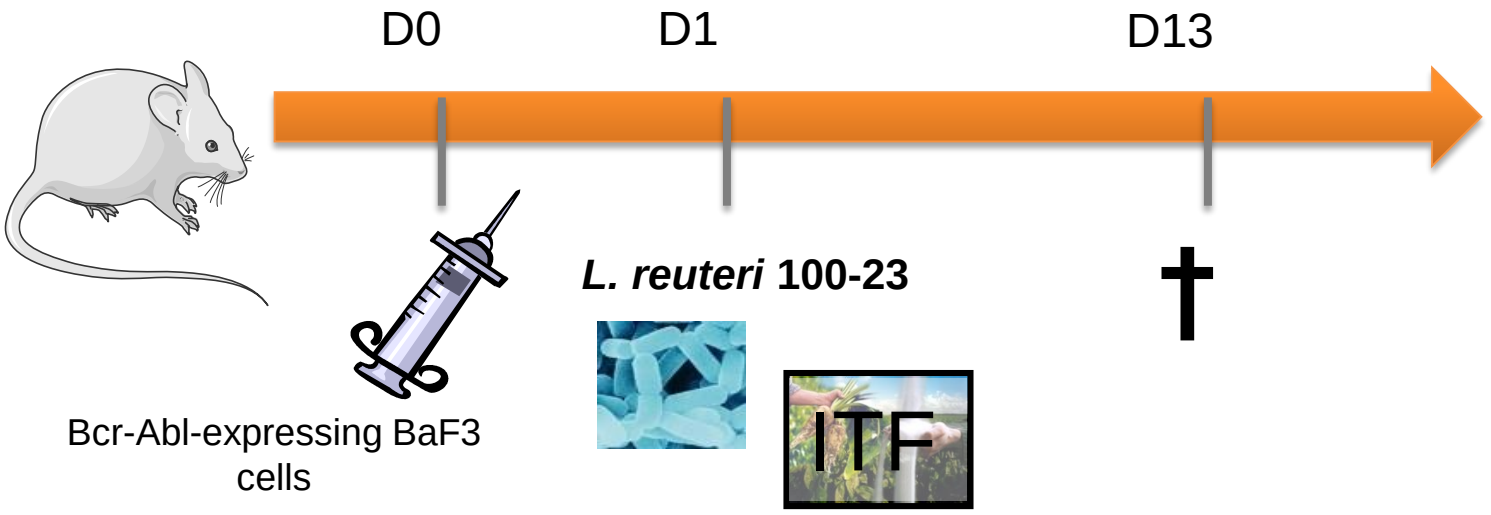
Increases portal propionate



Bindels et al Br J Cancer 2012

Propionate inhibits BaF3 cells proliferation *in vitro*

Selected synbiotic approach



Cachexia

Gut microbiota

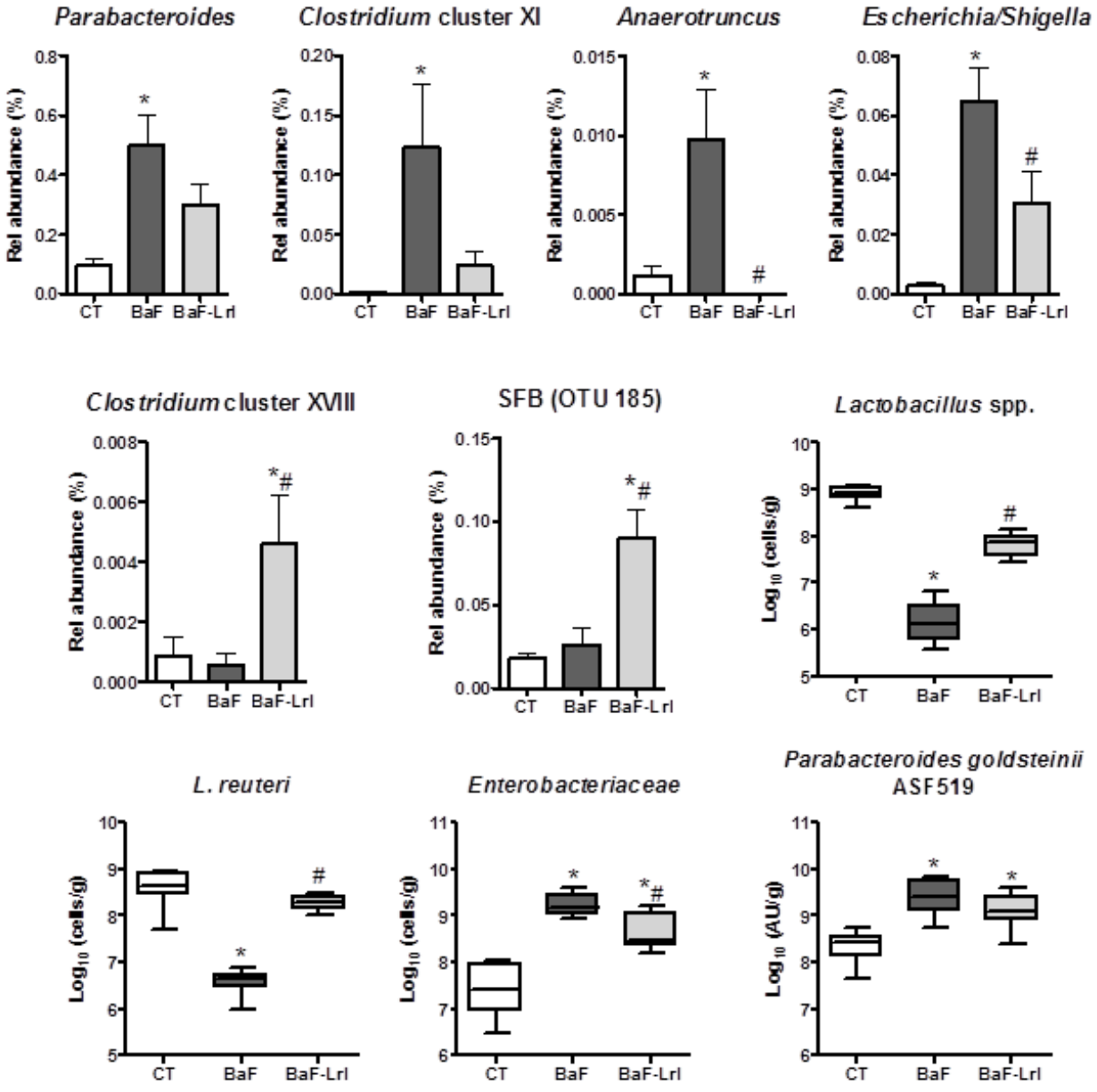
Portal metabolome

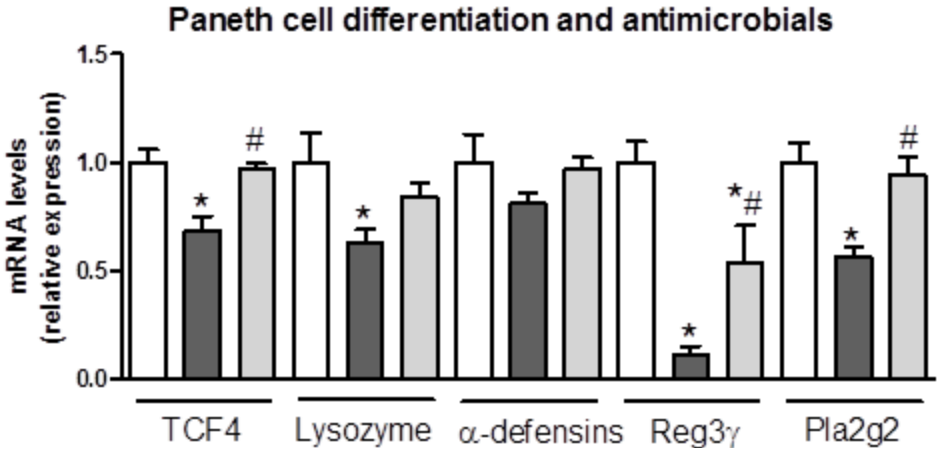
Cancer progression

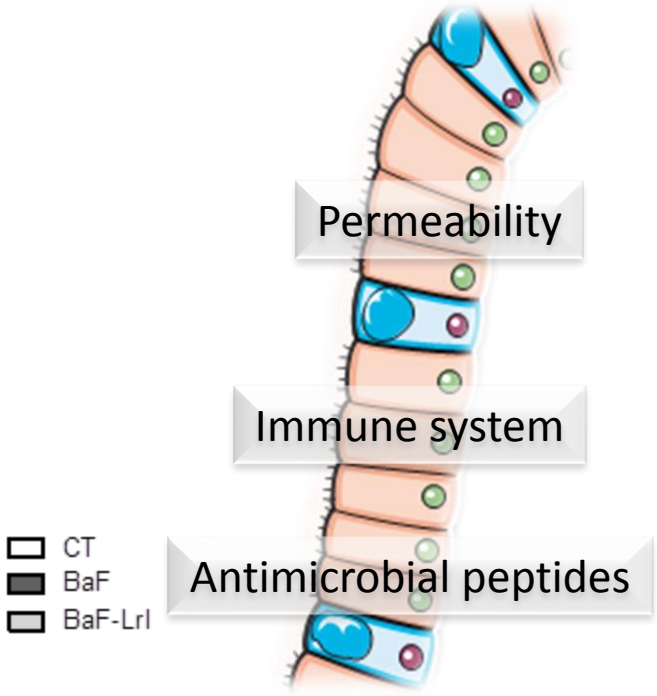
Barrier function

Survival

Bindels et al., The ISME J, *2015*


Parabacteroides
Clostridium cluster XI
Anaerotruncus
Escherichia/Shigella
Rel abundance (%)
CT
BaF
BaF-Lrl
Clostridium cluster XVIII
SFB (OTU 185)
Lactobacillus spp.
Log10 (cells/g)
L. reuteri
Enterobacteriaceae
Parabacteroides goldsteinii ASF519
Log10 (AU/g)

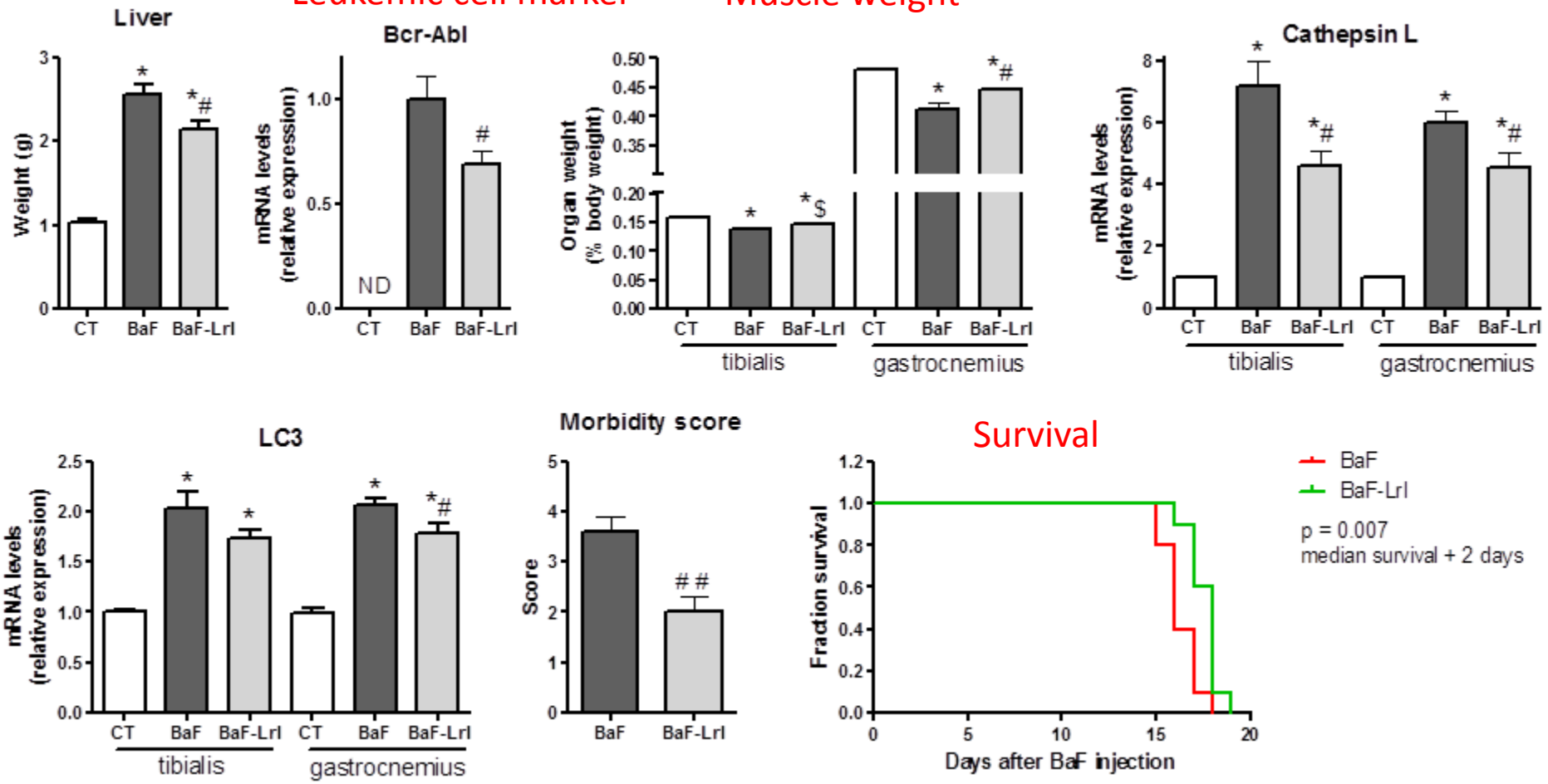

Paneth cell differentiation and antimicrobials
mRNA levels (relative expression)
1.5
1.0
0.5
0.0
TCF4
Lysozyme
α-defensins
Reg3γ
Pla2g2


Permeability
Immune system
Antimicrobial peptides
CT
BaF
BaF-Lrl

Benefits of the « synbiotic » approach

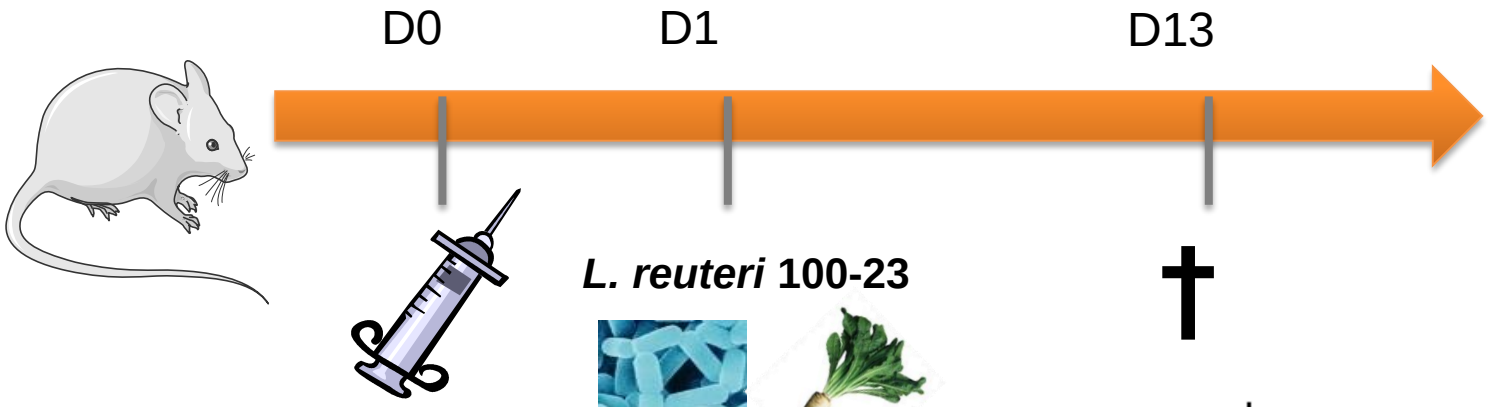
Leukemic cell marker

Muscle weight



Bindels et al., The ISME J, *2015*

Modulation of gut microbiota by probiotic and prebiotic controls cancer cachexia in a model of leukemia



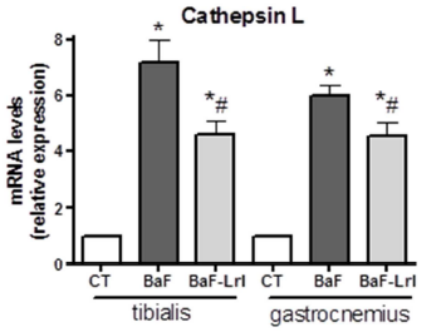
Survival

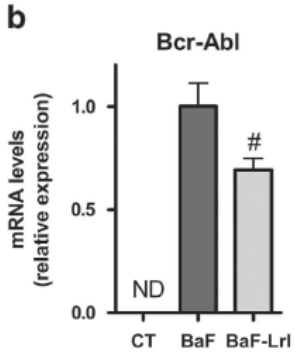
Gut microbiota

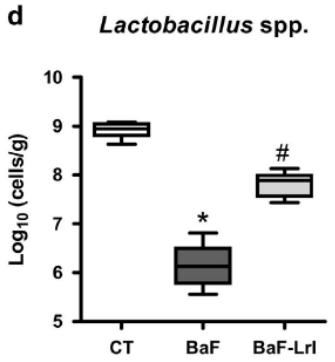
Cachexia

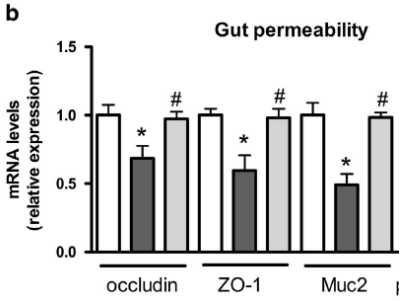
Barrier function

Tumor Proliferation In the liver



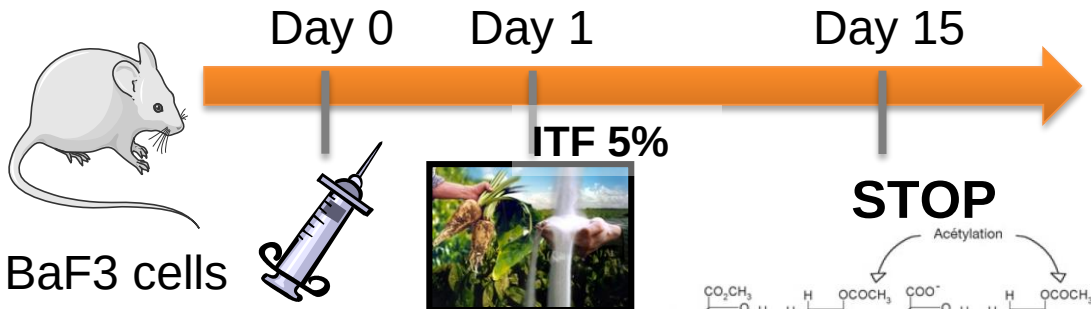






Bindels et al., The ISME J, *12/2015*

Novel prebiotics (pecto-oligosaccharides POS) avoid fat mass loss in cancer cachexia



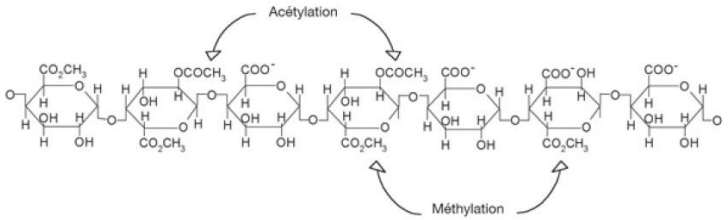
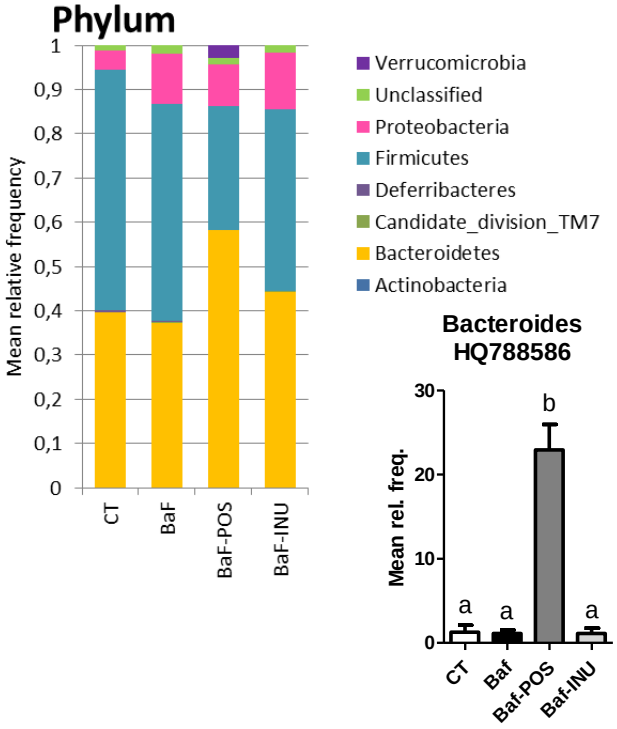
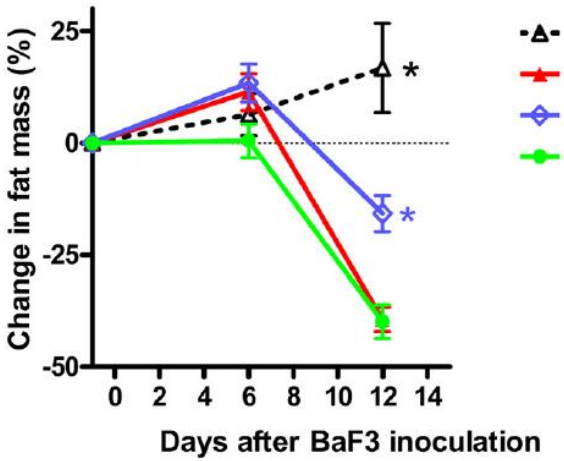
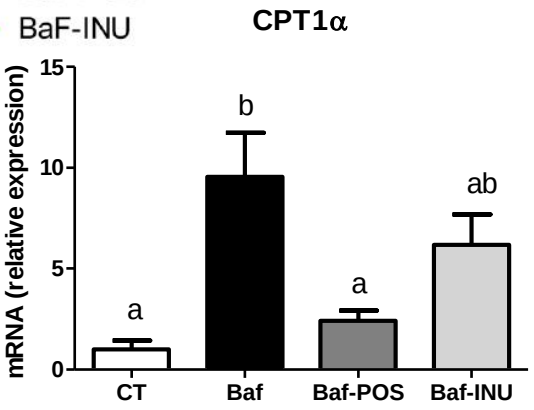


Figure 1. Structure primaire d'un homogalacturonane — *Primary structure of a homogalacturonan.*







Bindels, Neyrinck et al. Plos One 2015

Summary, future prospects

- In models of cancer cachexia, common bacterial changes are observed (increase in *Enterobacteriaceae*, *Parabacteroides goldsteinii* , decrease in *Lactobacilli*, in richness and evenness, those changes being independent on food intake.
- Disturbances of the gut barrier function (incl. immunity) , which could participate to the systemic inflammation and thereby influence host health.
- Experimental studies support the interest of probiotic and prebiotic approaches in this context.
- Future projects : focus on dysbiosis and inflammation in **patients** presenting acute myeloïd leukemia – association with cachexia

MicroAML

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