Understanding the mechanism of action of prebiotics in metabolic health
An overview of WP5 activities
N.M. Delzenne
Starting point: defining obesity and related metabolic disorders

- Obesity is an inflammatory disease
- Obesity is a « microbial »-related disease
- Obesity is a « brain » (behavioral) disease
Dysbiosis is a driver inflammation, namely by disrupting the gut barrier
(translocation of LPS = α, 16S rDNA, lipoteichoic acid)

Cani et al Gut Microbes, 2012
Everard et al, PNAS 2013

Bifidobacteria
Akdermansia
Bacterial Diversity

Disturbed Mucus production

LPS increases
In diabetic patients

Cani et al Gut Microbes, 2012
Everard et al, PNAS 2013
Complex carbohydrates

Primary conjugated bile acids

Gut Barrier
↑
Endotoxemia

Intestinal transit

appetite

Insulin secretion/response

Goblet cell
Mucus production

Gpr41

Glp-2

PYY

Glp-1

L cell

Gpr43/41

Tgr5

H2S

Sulfide

Acetate
Propionate
Butyrate

Gut microbial activity

Negative impact of obesity/diabetes-related dysbiosis

Delzenne et al modified from Diabetologia, in revision
Starting point: defining obesity and related metabolic disorders

- Obesity is an inflammatory disease

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Can we target the gut microbiota to improve host health in the context of obesity and related metabolic disorders? How does it work?
Dysbiosis associated with obesity and related metabolic diseases

Modified from Lozupone et al., Nature 2012
### Concept of prebiotics

<table>
<thead>
<tr>
<th>Definition</th>
<th>Substantiation of prebiotic effect</th>
<th>Compounds</th>
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</thead>
<tbody>
<tr>
<td><strong>2010</strong></td>
<td>[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]</td>
<td>Selectivity of effect on gut microbiota should be established <em>in vivo</em> 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.</td>
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| **2015**   | A nondigestible compound that, through its metabolism 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 metabolism 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 |

*Bindels L, Delzenne N, Cani P, Walter J. Nature Reviews Gastroenterology and Hepatology online 2015 p. 7*
Prebiotics (Fructans, arabinoxylans, other fermentable fibers…) have beneficial effects for health in the context of obesity.

- Improve key intestinal functions
- Decrease endotoxemia (LPS level) and inflammation
- Decrease food intake (satiety)
- Lessen hepatic steatosis
- Decrease fat mass
- Lessen glycemia


Also shown in human Intervention studies
Future investigations: tools to study gut functions associated with improvement of host health by prebiotics.

Bacterial changes by prebiotics participate to the modulation of gut endocrine function.

How does it work?

GLP-2

+ Intestinal barrier

Decreased LPS, and inflammation

Low glycemia, satiety

Cani et al Diabetes 2007, Gut 2010
Diet quality impacts mental health

Fast-food and commercial baked goods consumption and the risk of depression

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• Longitudinal study over 2 years
• 3040 Australian adolescents, aged 11 – 18 years

A role for endocrine Peptides (PYY) ?

Are gut microbiota the intermediates?

• Longitudinal study over 2 years
• 8964 Spanish participants
Prebiotics can reinforce the gut barrier, How does it work? Is gut barrier a key target in obesity?

Zonula occludens 1 (ZO1) expression in the colon in mice fed a control diet (CT), a high fat diet (HF) or a HF diet supplemented with arabinoxylan oligosaccharides (HF-AXOS) for 8 weeks.

Representative blot of occludin protein expression from insoluble cellular fraction in the jejunum of mice fed a CT, HFD or HFD-META060 diet.

Representative immunofluorescence staining and immunohistochemistry score of the jejunum epithelial tight-junction proteins (occludin) in wild-type (CT), Ob-CT, Ob-Cell or Ob-Pre mice.
Is alteration of gut barrier a phenomenon dependent on the bacterial environment?

- Data (TUM) showed no impact of HFD on gut barrier function and intestinal/local inflammation independently of fat quantity/quality or feeding duration in our “hygienic controlled environment”

- New approach: transfer to human situation in a controlled environment: to create a humanized mouse model with different (lean vs. obese) human donors and dietary challenges
Holst and Deacon *Diabetologia* (2005)

- Differentiation
- Expression of proglugagon/pre-proPYY
Gut-liver axis

Interest of metabolomic approach
to innovate in the evaluation of bioactive bacterial metabolites

S. Claus (U Reading)
WP5 ….. Key objectives

1. To identify a protective microbiota, derived metabolites and specific key (core) bacteria for preventing the development of diet-induced obesity and metabolic dysfunction using biologic samples from previous human studies for selective mouse colonization in preclinical trials (animal models)

2. To identify the mechanism by which the human intestinal microbiota and specific key (core) bacteria influence inflammation and gut barrier functions in humanized obesity models

3. To identify the mechanism by which the intestinal microbiota, derived metabolites and specific key (core) bacteria interact with host endocrine gut functions influencing obesity

4. To evaluate the role of protein-derived bacterial metabolites on gut immunity and epithelial integrity

5. To identify the mechanism by which intestinal microbial-derived metabolites interact with the gut and liver cells to modulate systemic immunity and energy metabolism.

6. To identify the mechanisms by which the intestinal microbiota and specific key (core) bacteria modulate the gut-brain axis, thereby influencing brain function (e.g. ingestive behaviour)

7. To identify the role the intestinal microbiota and key (core) bacteria play in insulin resistance and metabolic impairment of the brain

QUESTIONS?