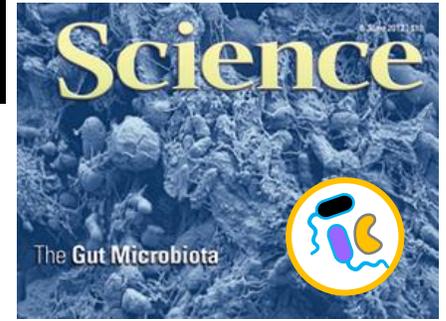
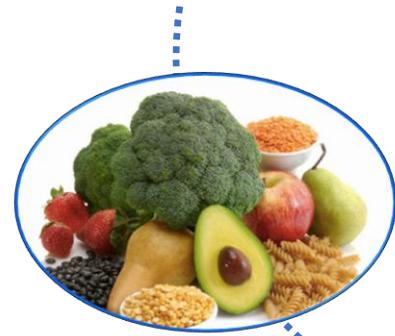
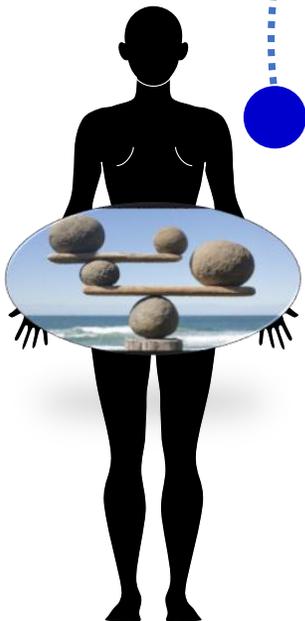


**RELACIÓN ENTRE LA MICROBIOTA
INTESTINAL Y LA SALUD Y
CONTRIBUCIÓN DE LA FIBRA EN LA DIETA**



OVERVIEW

- 1 GUT MICROBIOTA
- 2 GUT MICROBIOTA & DISEASES. OBESITY
- 3 MICROBIOME-BASED INTERVENTIONS FOR PROMOTING METABOLIC HEALTH.
PREBIOTICS & PROBIOTICS
- 4 MICROBIOTA-BY-DIET INTERACTION. SCFAs
- 5 GUT MICROBIOTA-HOST COMMUNICATION
- 6 GROUP OF MICROBIAL ECOLOGY, NUTRITION AND HEALTH.
'On the way to evaluate new probiotics'
- 6.1 Evaluation of the potential probiotic *Bacteroides uniformis* CECT 7771
- 6.2 Evaluation of dietary fiber supplementation (WBE) combine with
B. uniformis CECT 7771 intervention

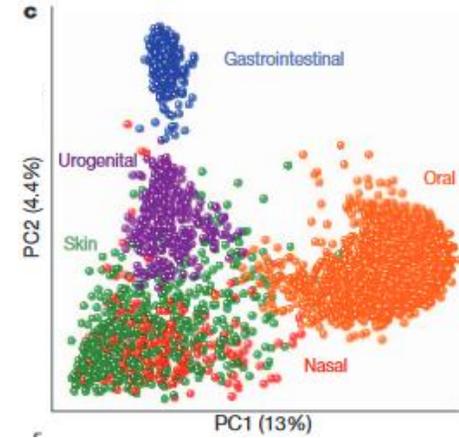


1. GUT MICROBIOTA

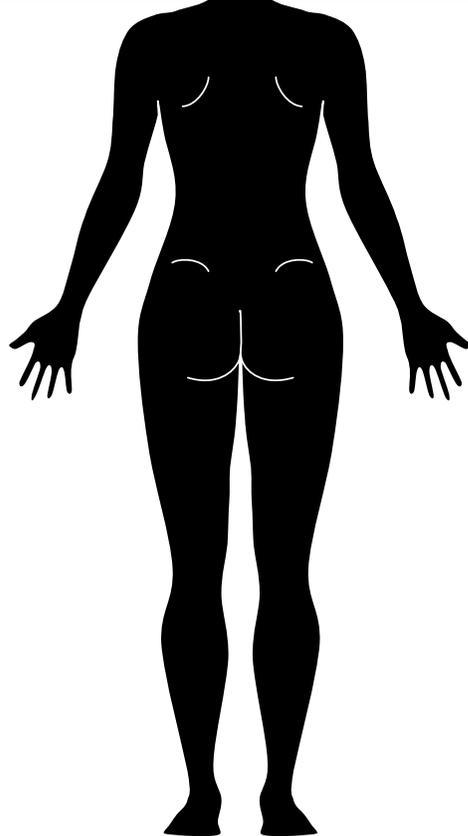
**39 trillion
 microbial cells**
**1-3% of body
 mass**



**Body habitat
 groups**

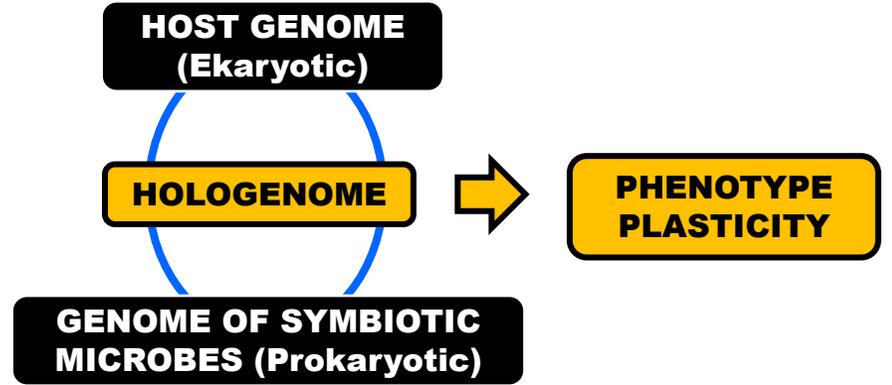


The Human Microbiome Project Consortium



**10 times more
 cells than
 human cells**

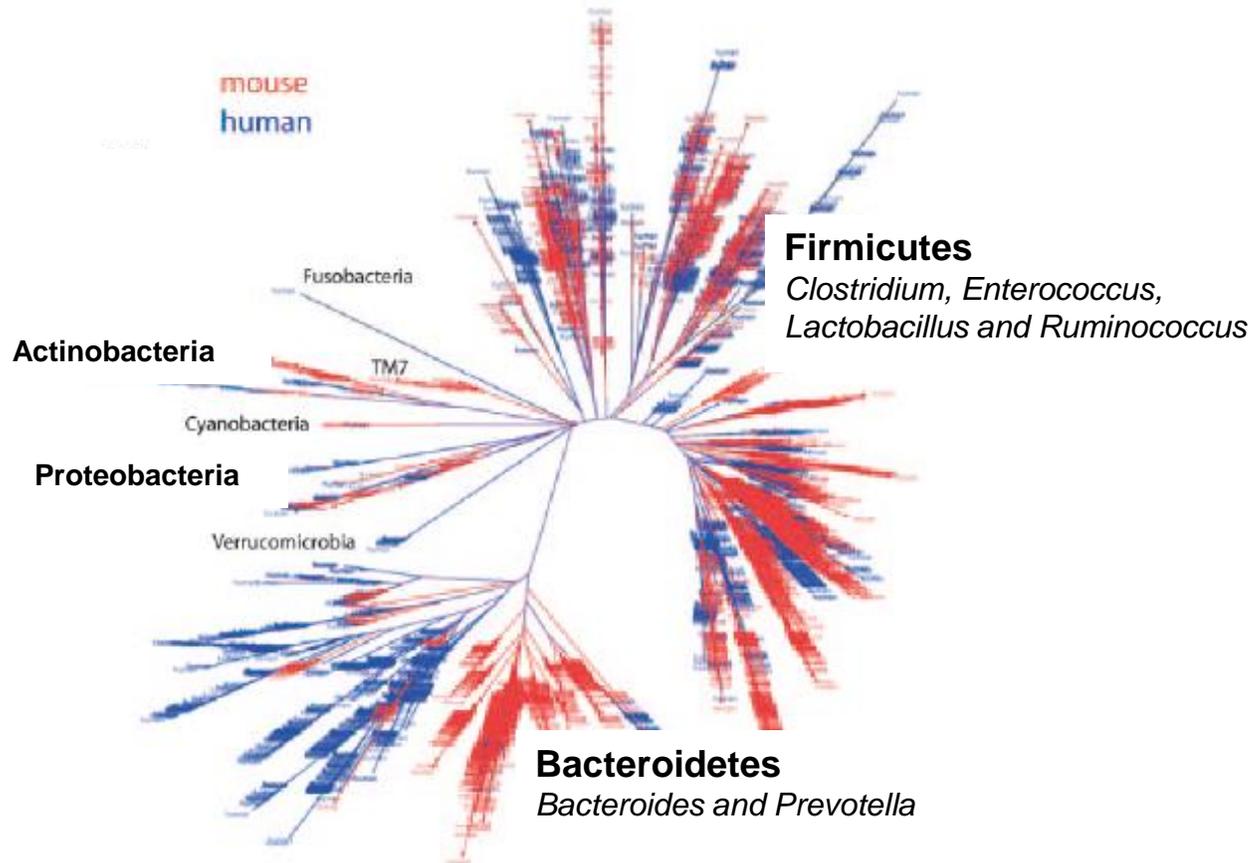
**150 times more
 genes than
 human genes**



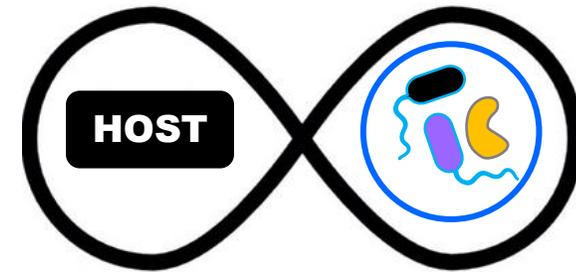
1. GUT MICROBIOTA



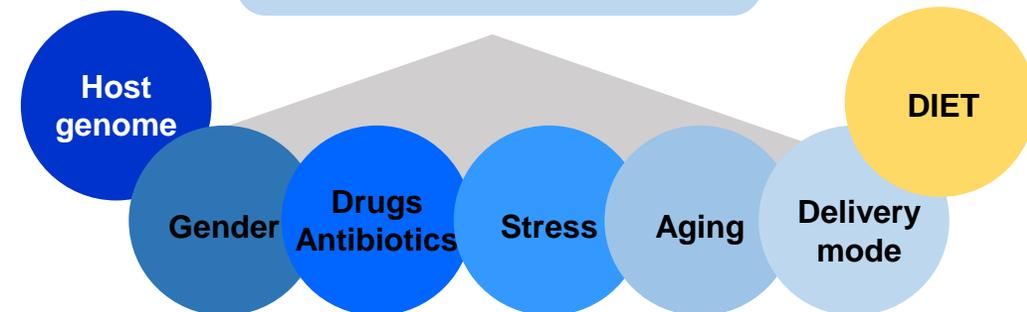
PHYLOGENY OF BACTERIAL PHYLA



SYMBIOSIS



Dynamic microbial community structure among individuals

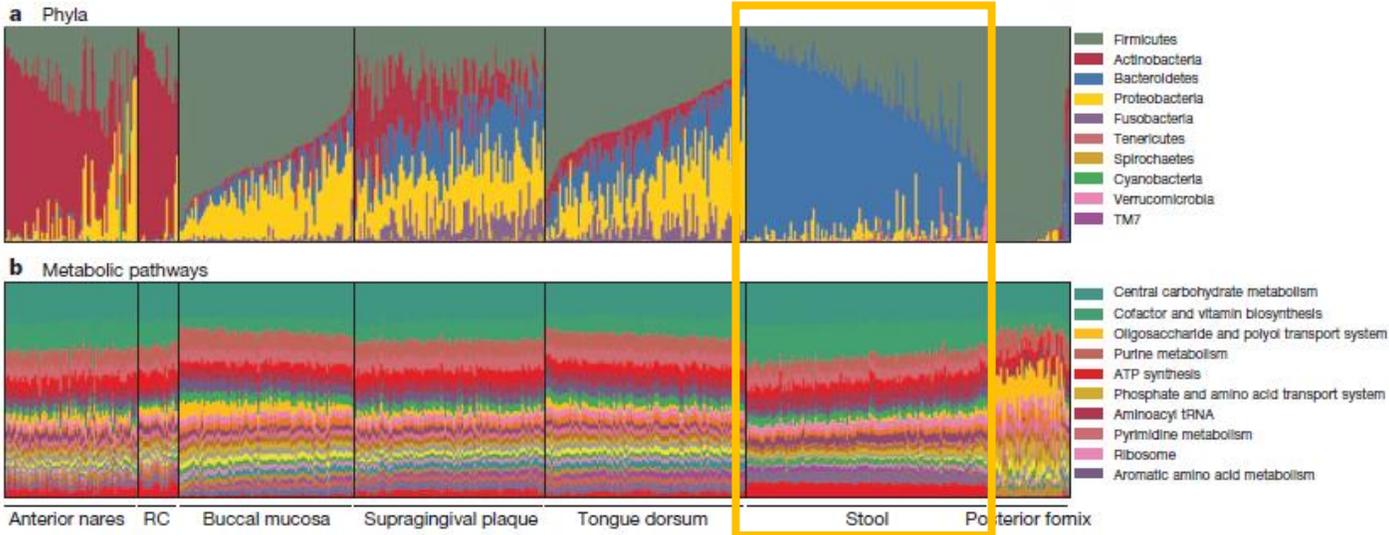


HOST PHENOTYPE PLASTICITY

1. GUT MICROBIOTA



Stability of metabolic pathways among individuals

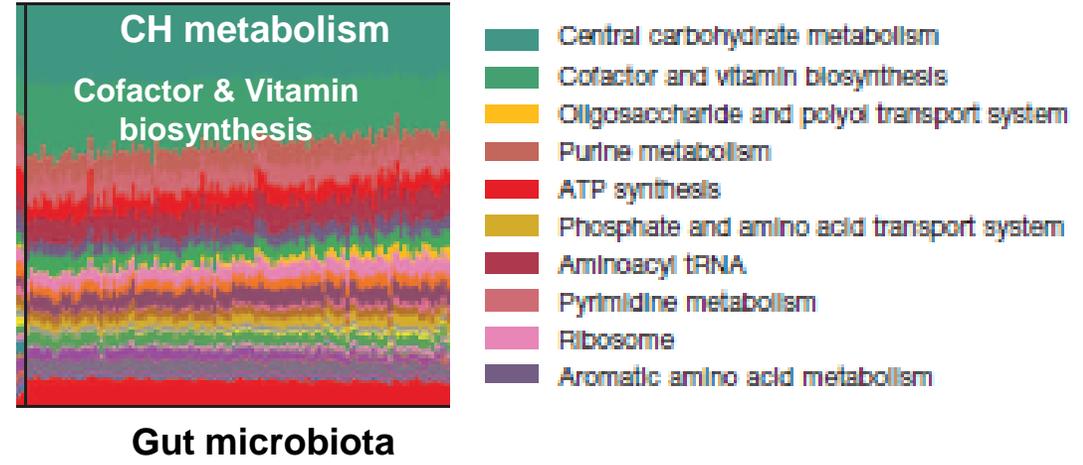
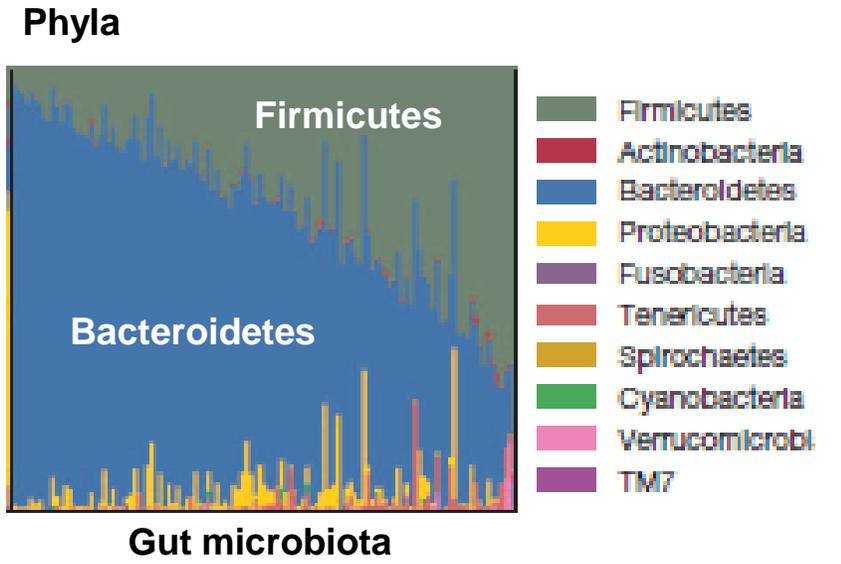


The Human Microbiome Project Consortium

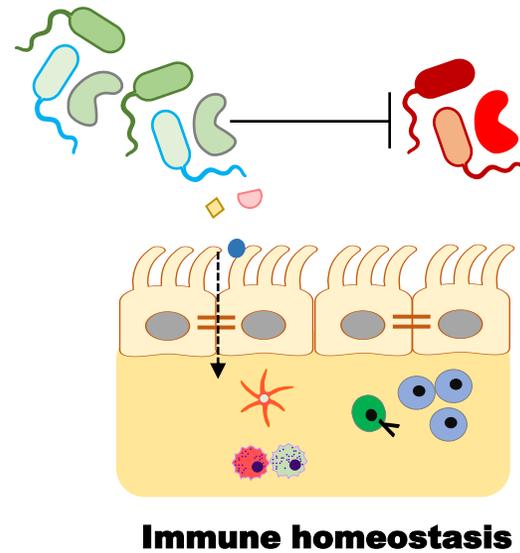
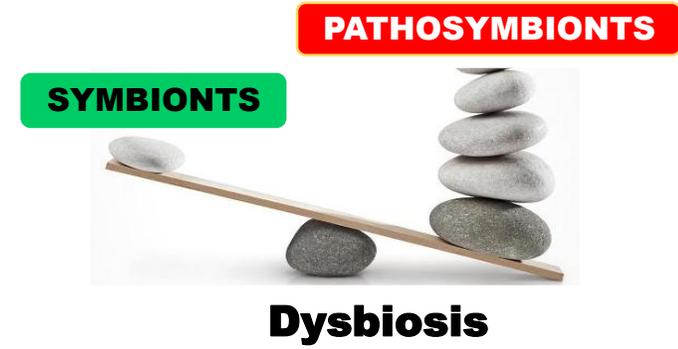
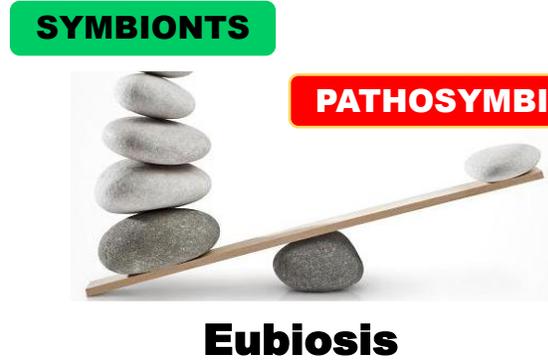
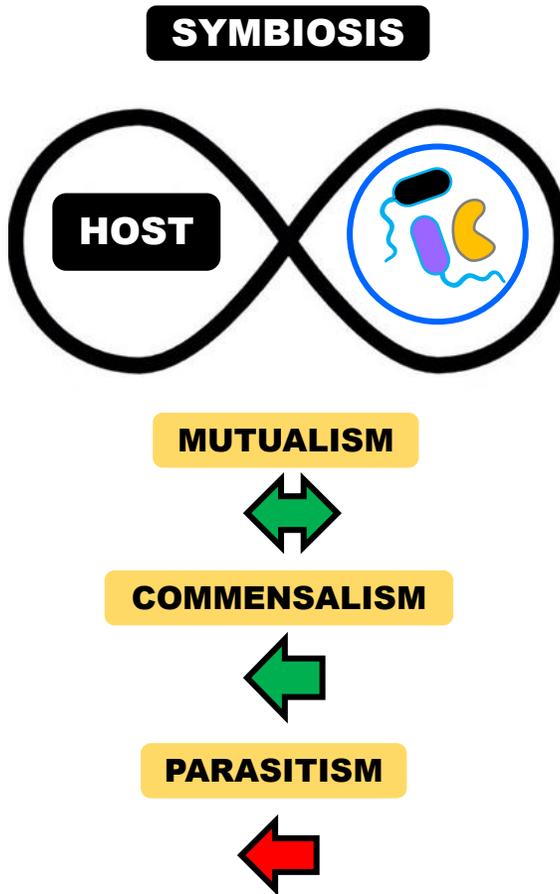


- **Energy harvest**
- **Protection against pathogens**
- **Immunomodulation**
- **Energy metabolic status**

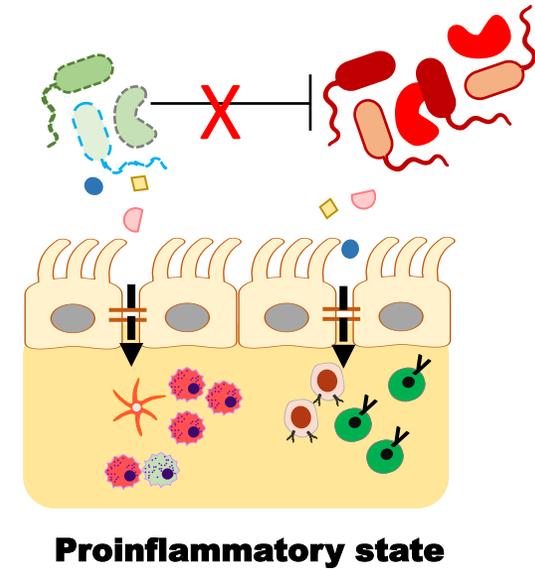
Nutrients Shelter



1. GUT MICROBIOTA & HOST



Healthy state



Intestinal and extra-intestinal Inflammatory DISEASES

-  DC
-  M1
-  M2
-  T cells
-  Treg
-  B cells



Dysbiosis

Proinflammatory state

PATHOSYMBIANTS

CHRONIC

SYMBIANTS



Intestinal and extra-intestinal Inflammatory DISEASES

- Inflammatory bowel disease
- Celiac disease
- Cardiovascular diseases
- Mental diseases (emotional, cognitive-related diseases; anxiety, depression, autism, etc)
- Metabolic diseases: Diabetes (T1D or T2D), Obesity, metabolic syndrome

A Pyrosequencing Study in Twins Shows That Gastrointestinal Microbial Profiles Vary With Inflammatory Bowel Disease Phenotypes

BEN P. WILLING,* JOHAN DICKSVED,* JONAS HALFVARSON,‡ ANDERS F. ANDERSSON,§¶ MARIANNA LUCIO,¶ ZONGLI ZHENG,‡ GUNNAR JÄRNEROT,‡ CURT TYSK,‡** JANET K. JANSSON,‡‡ and LARS ENGSTRAND§

GASTROENTEROLOGY 2010;139:1844-1854

The Duodenal Microbiota Composition of Adult Celiac Disease Patients Is Associated with the Clinical Manifestation of the Disease

Pirjo Wacklin, PhD,* Katri Kaukinen, MD,† Elina Tuovinen, MSc,* Pekka Collin, MD,† Katri Lindfors, PhD,‡ Jukka Partanen, PhD,* Markku Mäki, MD,‡ and Jaana Mättö, PhD*

(Inflamm Bowel Dis 2013;0:1-8)

Psychosomatic Medicine

Author's Accepted Manuscript

Article Title: Brain-gut-microbiota axis in psychiatry: novel paradigm or false dawn?

Authors: Timothy G. Dinan and John Cryan

PSYCHOSOMATIC
MEDICINE

Journal of Biobehavioral Medicine
www.psychosomaticmedicine.org

Author Manuscript In Press

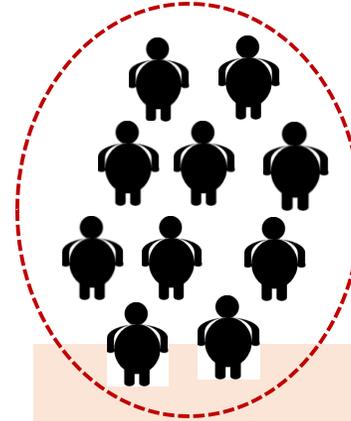
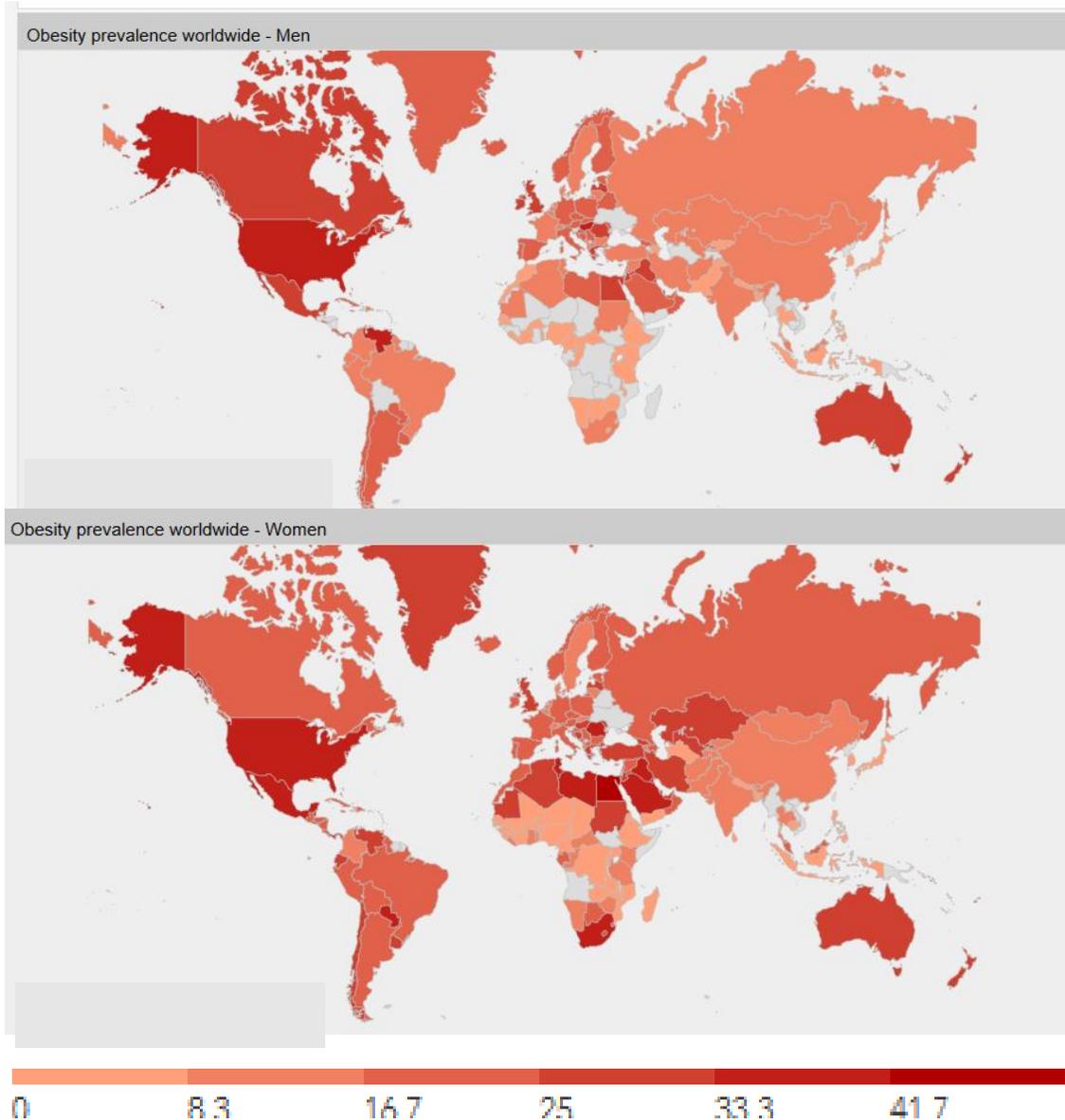
CellPress

Cell Metabolism
Article

Intermittent Fasting Promotes White Adipose Browning and Decreases Obesity by Shaping the Gut Microbiota

Guolin Li,^{1,2,3,7,*} Cen Xie,^{1,7} Siyu Lu,² Robert G. Nichols,⁴ Yuan Tian,⁴ Lichen Li,² Daxeshkumar Patel,¹ Yinyan Ma,⁵ Chad N. Brocker,¹ Tingting Yan,¹ Kristopher W. Krausz,¹ Rong Xiang,⁵ Oksana Gavrilova,⁵ Andrew D. Patterson,⁴ and Frank J. Gonzalez^{1,3,*}

2. GUT MICROBIOTA & OBESITY



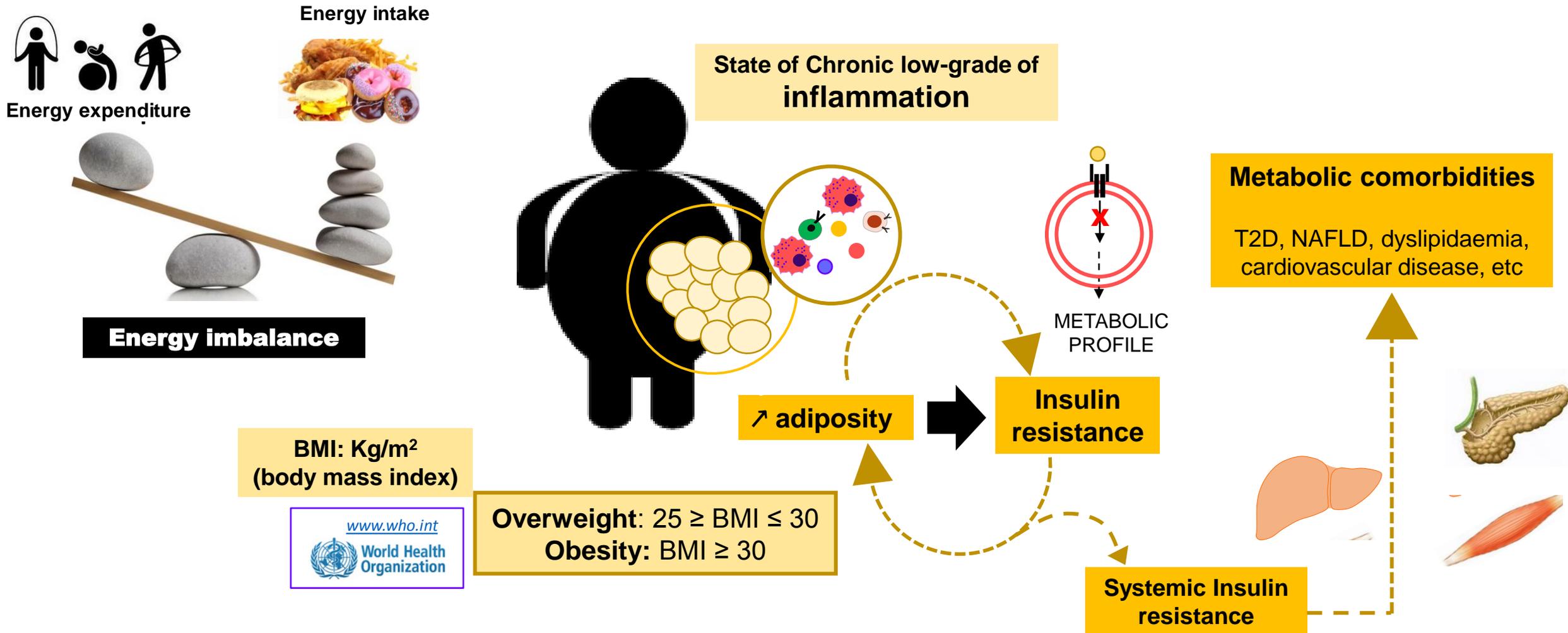
KEY FACTS OF OBESITY

- ↗ prevalence from 1975 (x3)
- In 2016:
 - ADULTS: 39% overweight and 13% obese.
 - CHILDREN & ADOLESCENTS: 18% overweight or obese
- Obesity ranks fifth in risk of global deaths in the general population
- ↗ prevalence in low and middle-income countries
- **OBESITY IS PREVENTABLE**



2. GUT MICROBIOTA & OBESITY

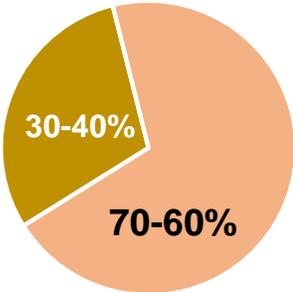
PATHOPHYSIOLOGY OF OBESITY



2. GUT MICROBIOTA & OBESITY



Genetic factors



Environmental factors

Sedentary life style

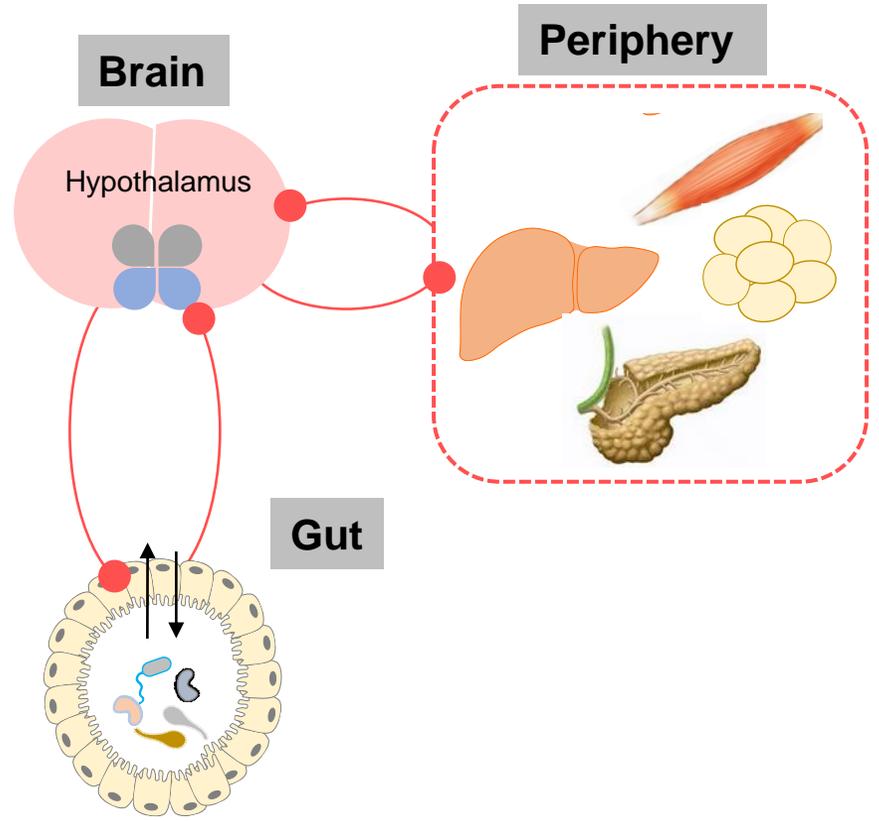
↓ satiety signals sensitivity

DIET: Energy-dense foods



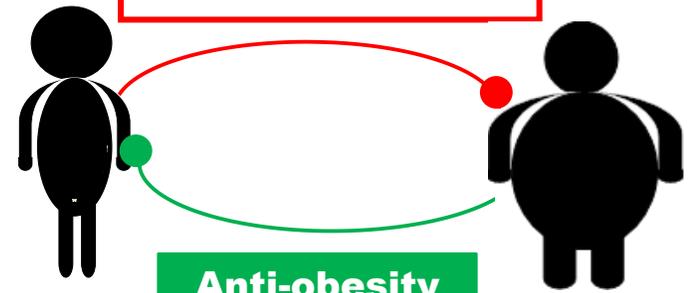
Gut microbiota

Gut-brain-periphery axis



ENERGY IMBALANCE

Over-eating
 ↑ adiposity
 Glucose intolerance
 Insulin resistance



Anti-obesity interventions

ENERGY BALANCE

Restoration of gut-brain communication

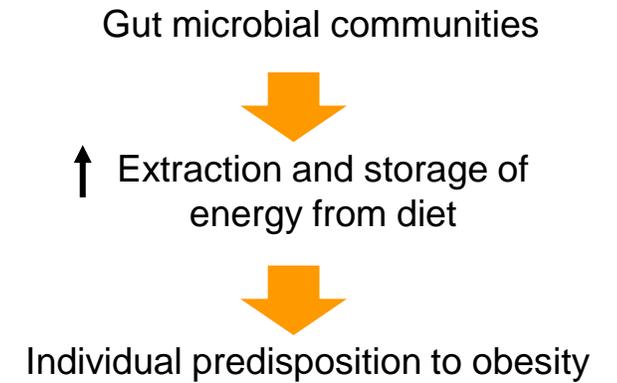
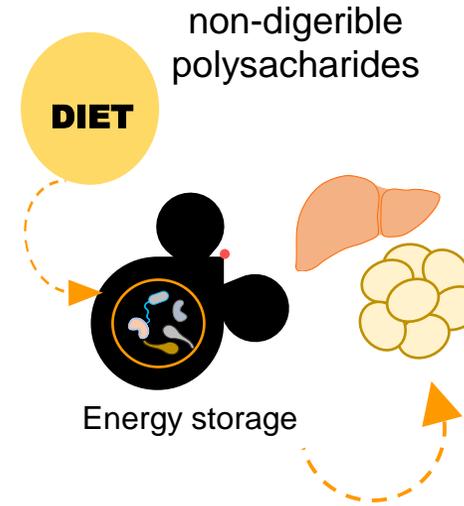
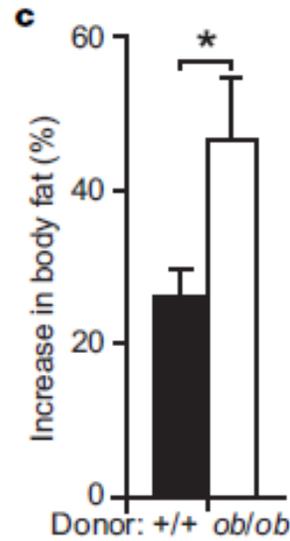
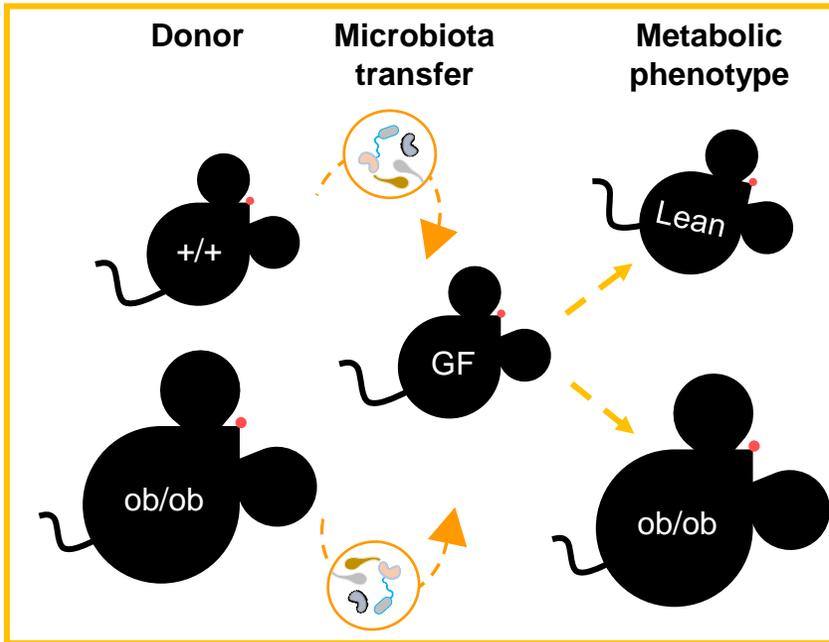
EUBIOSIS



nature

An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh¹, Ruth E. Ley¹, Michael A. Mahowald¹, Vincent Magrini², Elaine R. Mardis^{1,2} & Jeffrey I. Gordon¹

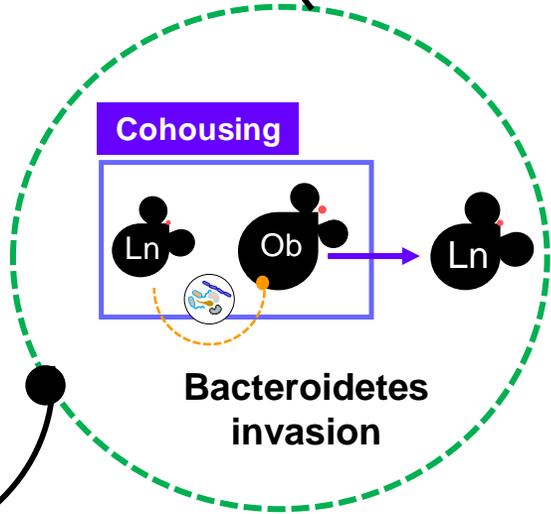
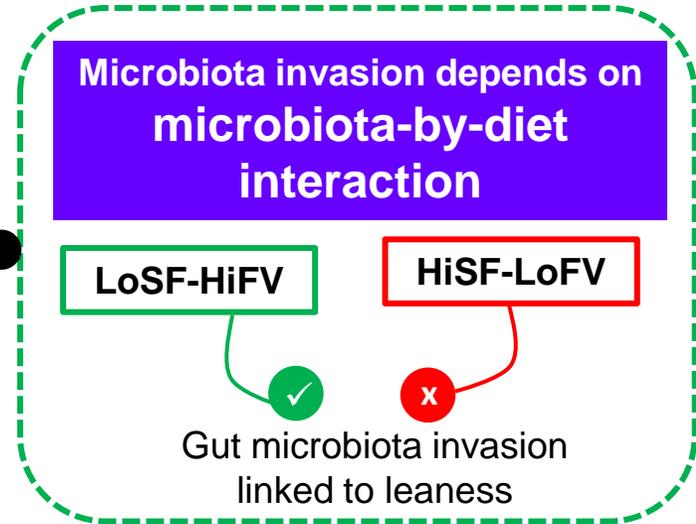
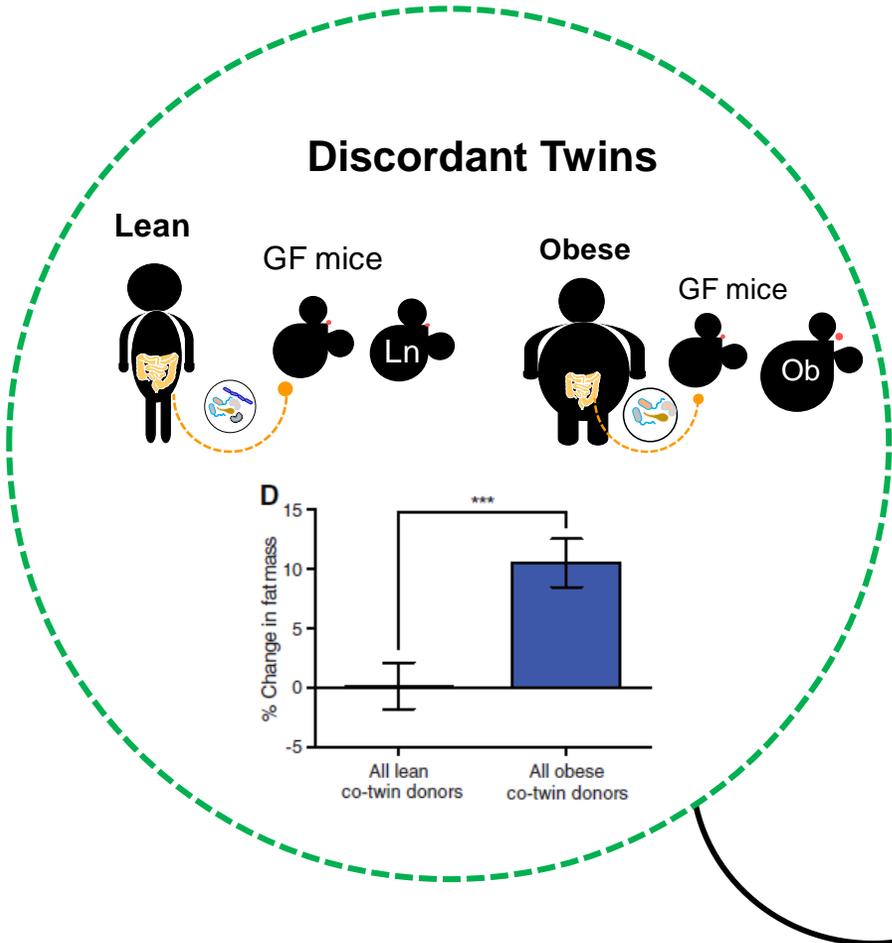


Gut microbiota is an environmental factor of obesity

2. GUT MICROBIOTA & OBESITY



Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice
 Vanessa K. Ridaura *et al.*
Science 341, (2013);
 DOI: 10.1126/science.1241214



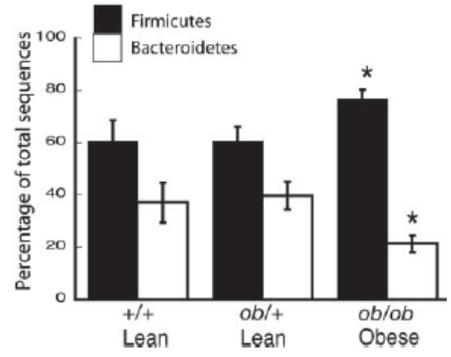
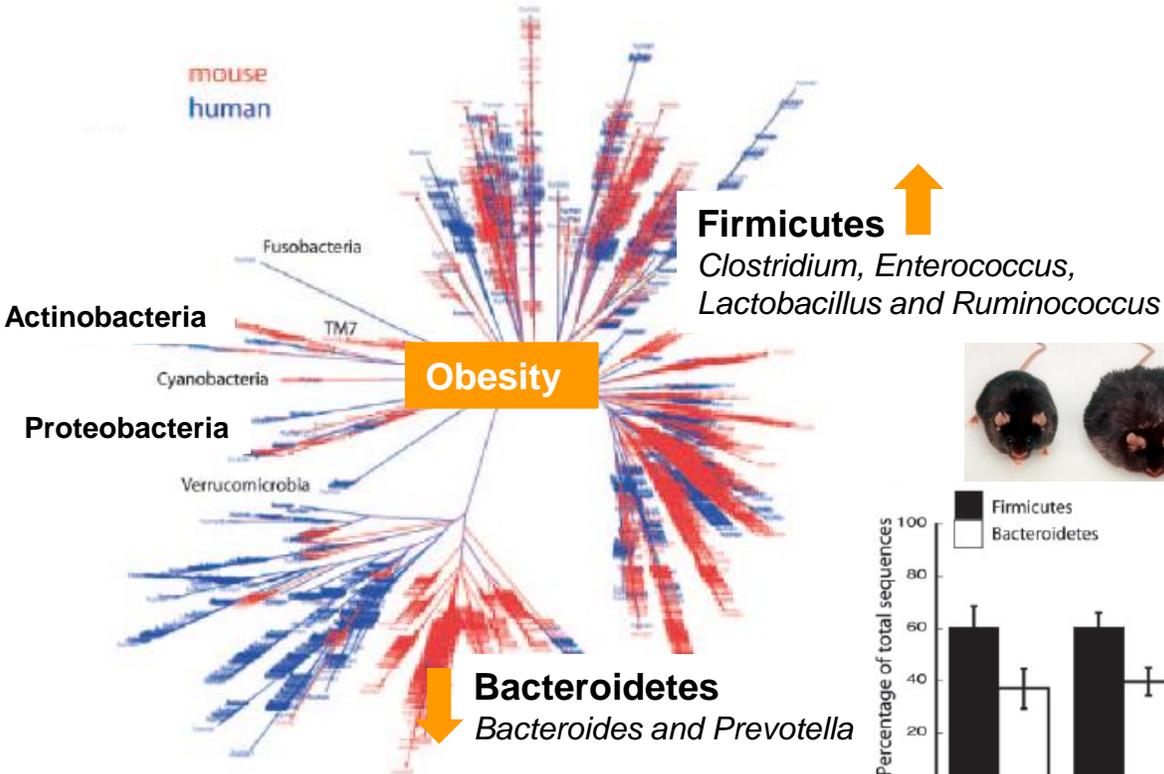
2. GUT MICROBIOTA & OBESITY



Obesity alters gut microbial ecology



Ruth E. Ley[†], Fredrik Bäckhed[†], Peter Turnbaugh[†], Catherine A. Lozupone[‡], Robin D. Knight[§], and Jeffrey I. Gordon^{†¶}

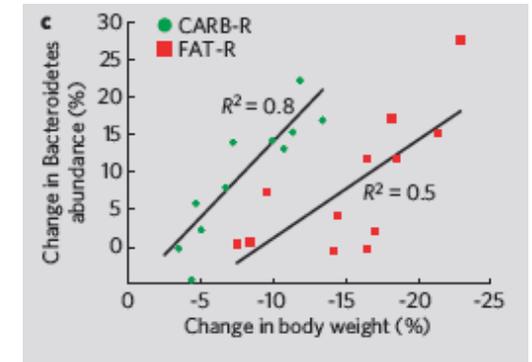
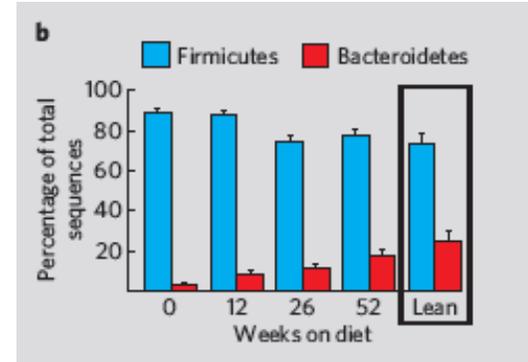


ob/ob 50% fewer Bacteroidetes

MICROBIALECOLOGY

Human gut microbes associated with obesity

Ley et al, Nature 2006



FAT-R, fat restricted
 CARB-R, carbohydrate restricted

Manipulation of microbial community structure

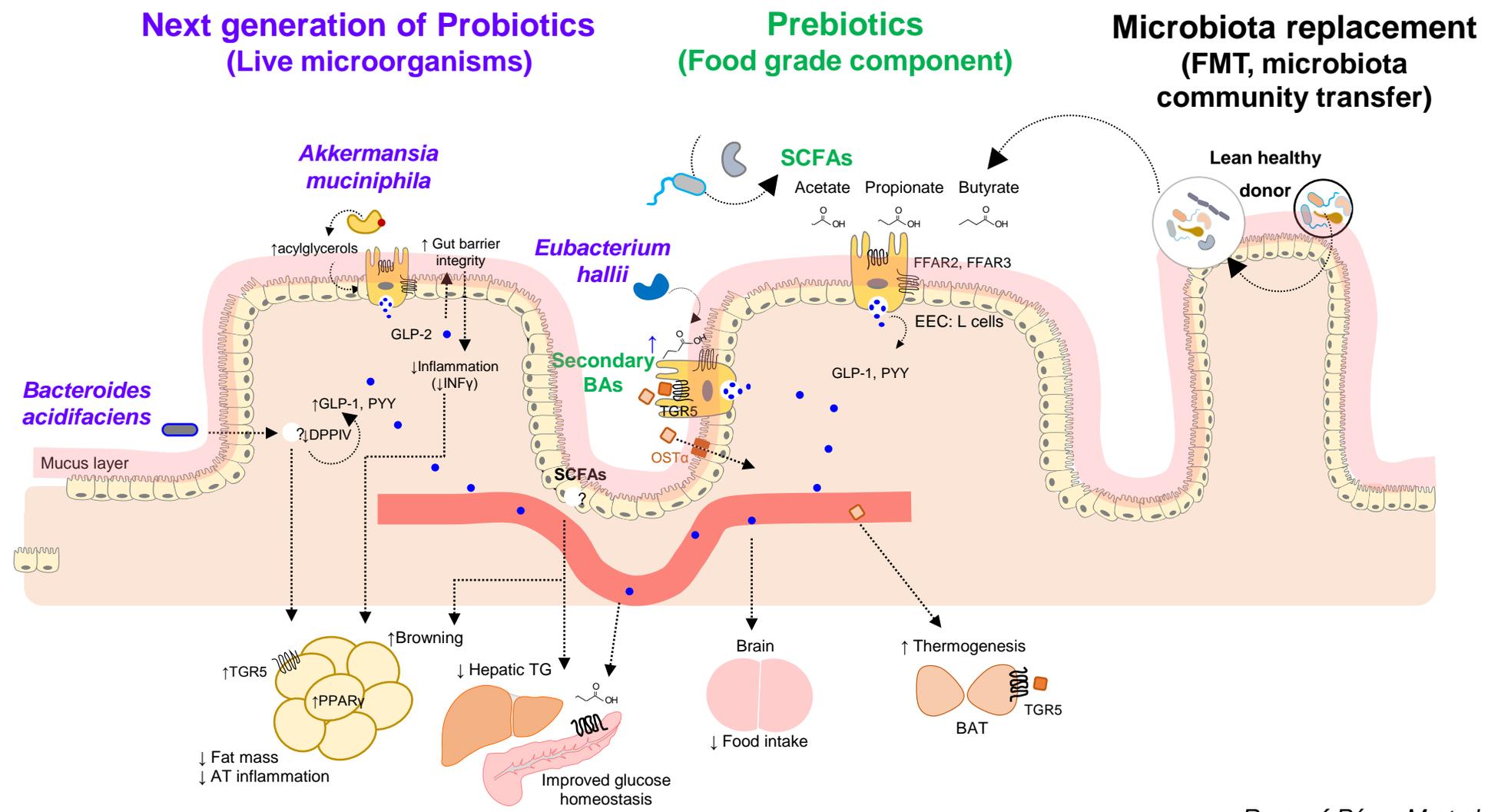
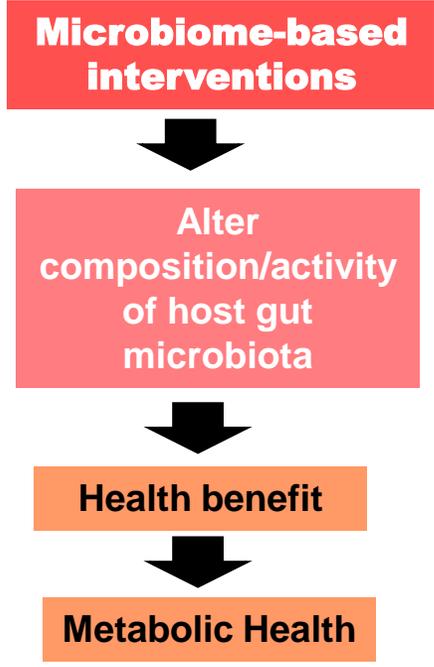
MICROBIOME-BASED interventions for promoting metabolic health

PREBIOTICS

PROBIOTICS

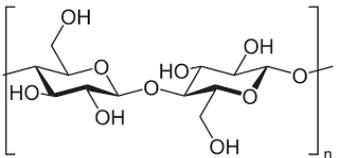
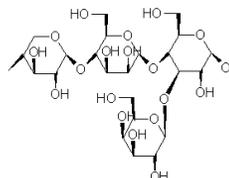
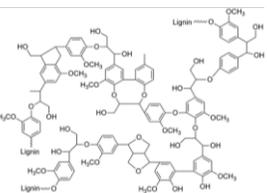
FECAL TRANSFER

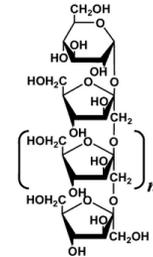
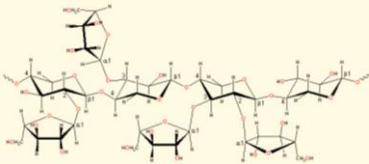
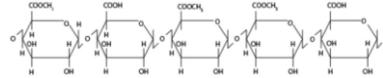
3. MICROBIOME-BASED INTERVENTIONS FOR PROMOTING METABOLIC HEALTH





DIETARY FIBER: indigestible plant polysaccharides

NUTRIENT	Natural SOURCE
Water-insoluble dietary fibers	
Cellulose 	 Cereals  Fruit  Vegetables
Hemicellulose 	 Cereals  Bran  Legumes
Lignin 	 Cereals  Garden beans
Resistant starch	 Corn  Wheat  Barley

NUTRIENT	Natural SOURCE
Water-soluble dietary fibers	
Inulin 	 Chicory root  Onion
Fructooligosaccharides (FOS)	 Leek  Banana
Arabinoxylan (Hemicellulose) 	 Cereals  Wheat
Arabinoxylan oligosaccharides (AXOS)	Non-starch polysaccharide (NSP) bran ~70% endosperm ~88%
Pectin 	 Fruits  Corn flakes  Carrots

3.2 PROBIOTICS



Food and Agriculture Organization of the United Nations



World Health Organization

Guidelines for the Evaluation of Probiotics in Food

Strain identification

Functional characterization

Safety assesment

in vitro & *in vivo*

Efficacy

Phase 2 human trial (DBPC).
Probiotic vs placebo

Effectiveness

Phase 3 human trial
Probiotic vs standard treatment

Probiotic for FOOD

'Classical' probiotics

- Currently commercialized probiotics
- Lactic acid bacteria and bifidobacteria
- Biological samples or derived from fermented foods

Next Generation of Probiotics (NGP)

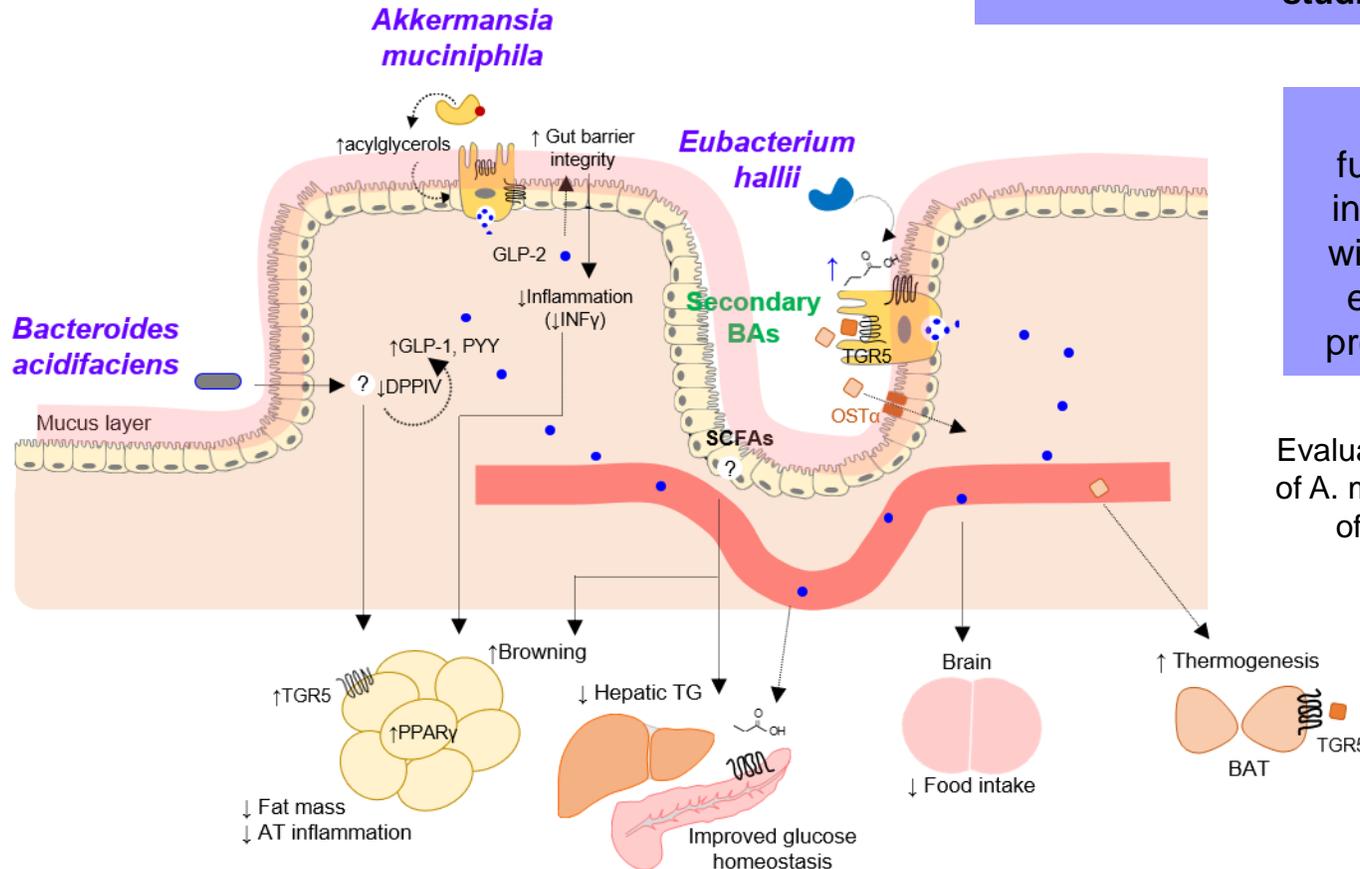
Massive use of DNA sequencing in controlled (16S rRNA gene-based approach, whole-genome shotgun-based approach) **epidemiological studies**

NGP: Selected functionally distinct indigenous bacteria with potential higher efficacy of current probiotic formulation

Evaluation of the administration of *A. muciniphila* on parameters of Metabolic Syndrome

ClinicalTrials.gov Identifier:
NCT02637115

Sponsor:
Patrice D. Cani

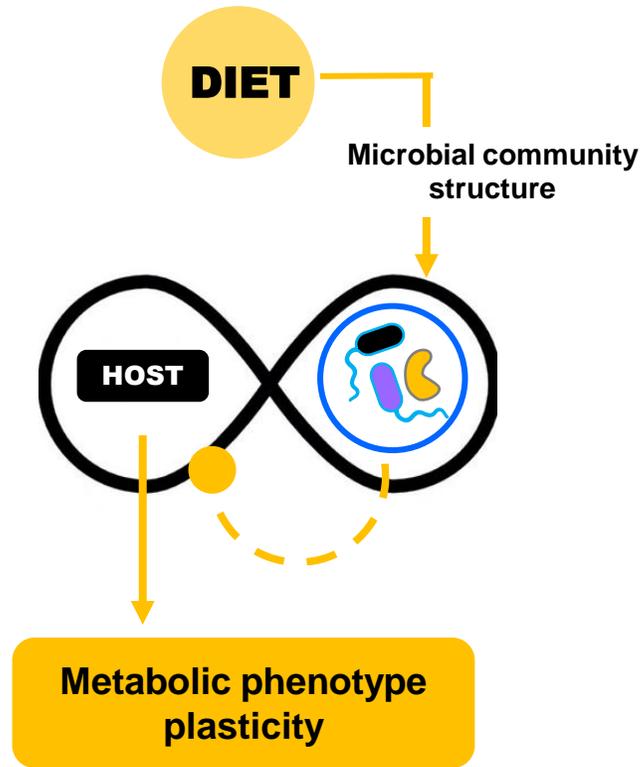


Romaní-Pérez M et al, 2017



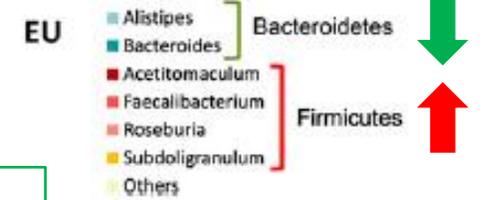
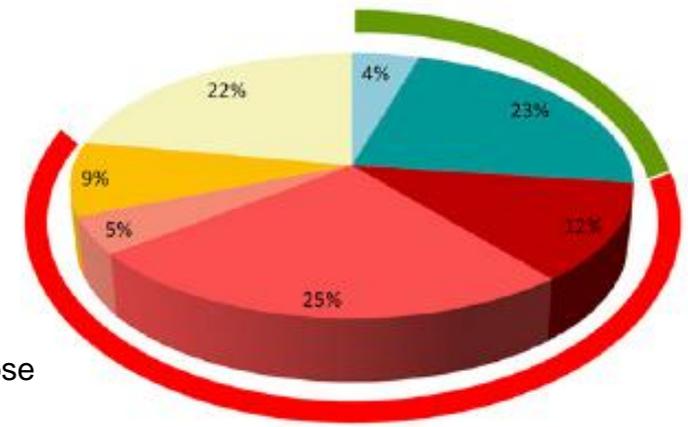
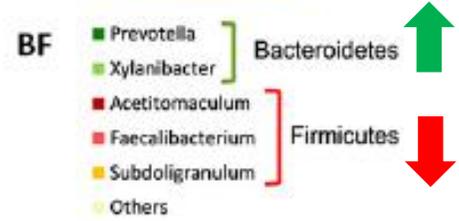
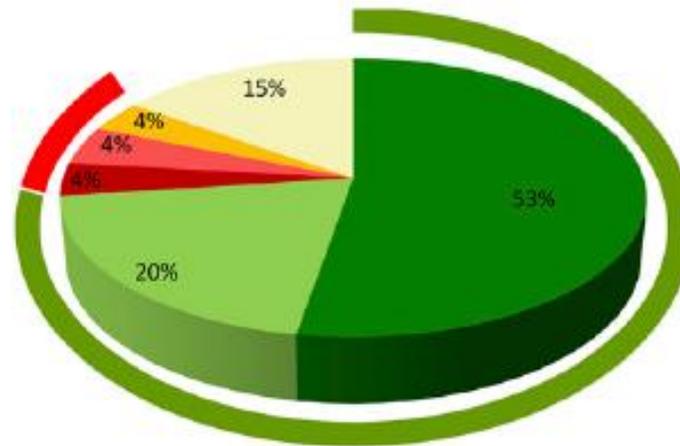
MICROBIOTA-BY-DIET INTERACTION

Different diets in human population

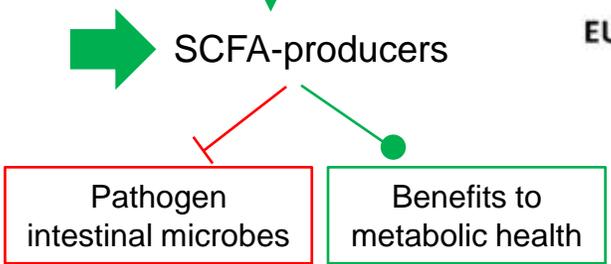


Burkina Faso children
DIET: high in FIBER and low in fat

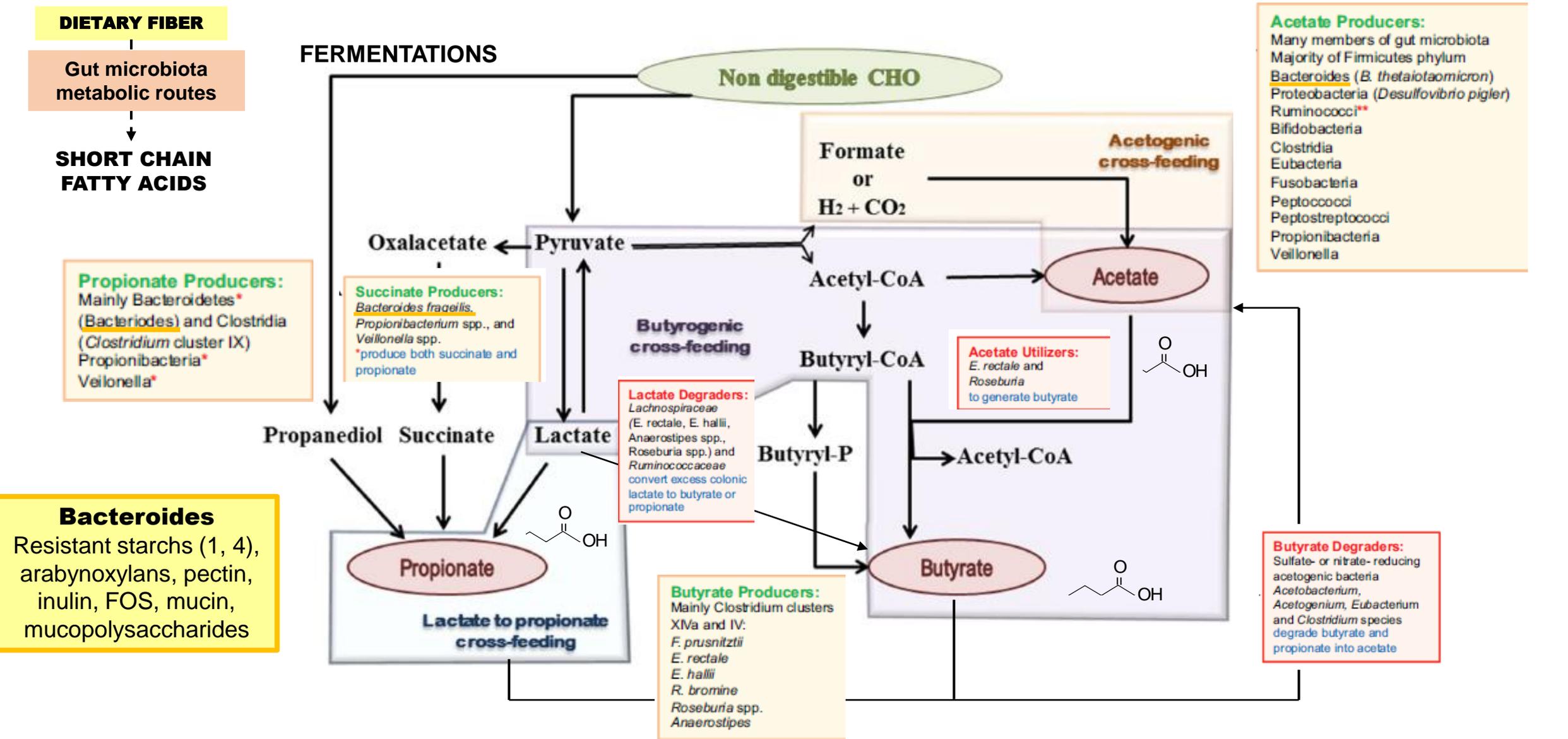
European children
DIET: high in animal PROTEIN, SUGAR and FAT. Low in fiber



Whole grains
 Dietary fiber
 ↓
 Xylane, xylose,
 carboxymethylcellulose
 ↓
SCFA-producers



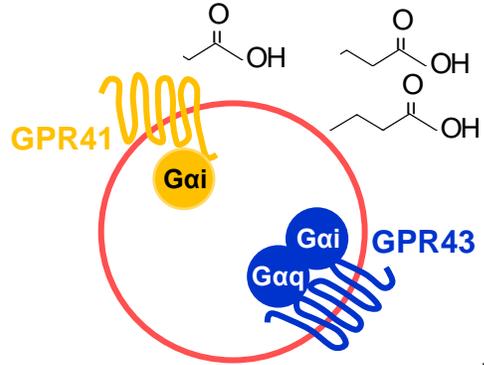
4. MICROBIOTA-BY-DIET INTERACTION. SCFAs



5. GUT MICROBIOTA-HOST COMMUNICATION



SCFAs: bioactive molecules

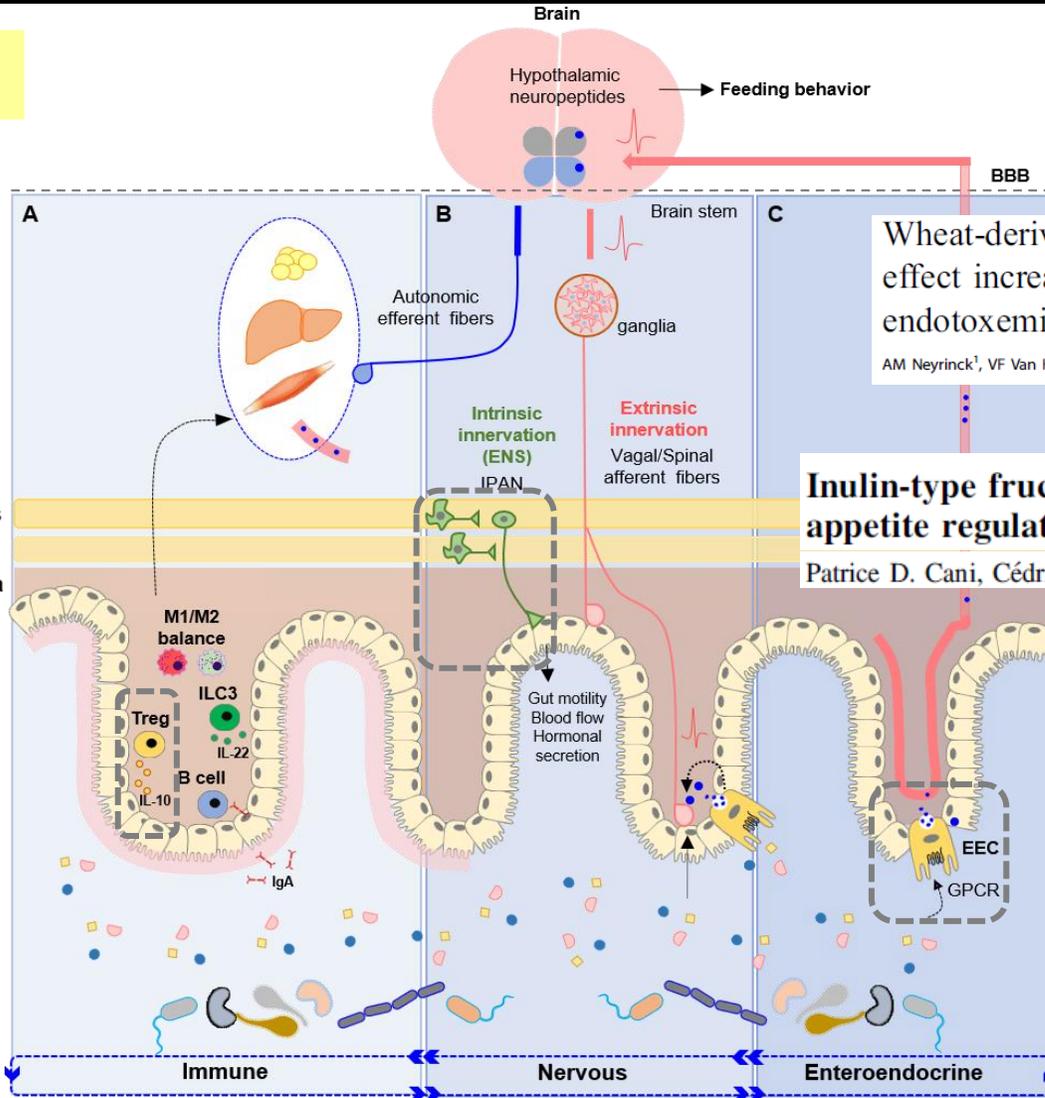
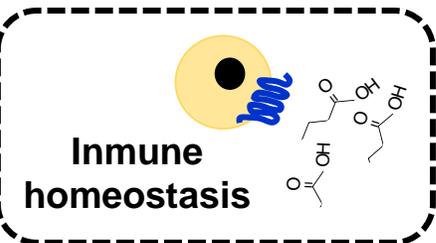


Cellular response

- Enteroendocrine cells
- Neurons
- Immune cells

The Microbial Metabolites, Short-Chain Fatty Acids, Regulate Colonic T_{reg} Cell Homeostasis

Patrick M. Smith,¹ Michael R. Howitt,¹ Nicolai Panikov,¹ Monia Michaud,¹ Carey Ann Gallini,¹ Mohammad Bohlooly-Y,⁵ Jonathan N. Glickman,^{6,7} Wendy S. Garrett^{1,2,3,4*}

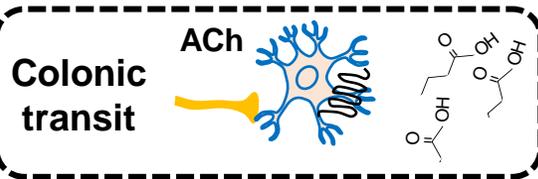
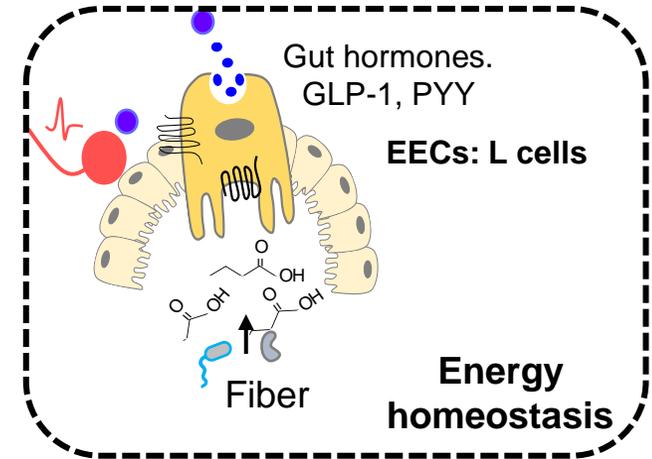


Wheat-derived arabinoxylan oligosaccharides with prebiotic effect increase satiogenic gut peptides and reduce metabolic endotoxemia in diet-induced obese mice

AM Neyrinck¹, VF Van Hée¹, N Piront², F De Backer¹, O Toussaint², PD Cani¹ and NM Delzenne¹

Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats*

Patrice D. Cani, Cédric Dewever and Nathalie M. Delzenne†



Short-Chain Fatty Acids Regulate the Enteric Neurons and Control Gastrointestinal Motility in Rats

RODOLPHE SORET,^{*,1,§,||} JULIEN CHEVALIER,^{*,1,§,||} PIERRE DE COPPET,^{1,§,||,¶} GUILLAUME POUPEAU,^{1,§,||,¶} PASCAL DERKINDEREN,^{*,4,§,||} JEAN PIERRE SEGAIN,^{1,§,||,¶} and MICHEL NEUNLIST^{*,4,§,||}

5. GUT MICROBIOTA-HOST COMMUNICATION IMMUNOMODULATION



Obesity → State of Chronic low-grade of inflammation

Adipose tissue

increased M1/M2 ratio

Cytotoxic T cells
Th1 and Th17

B cells

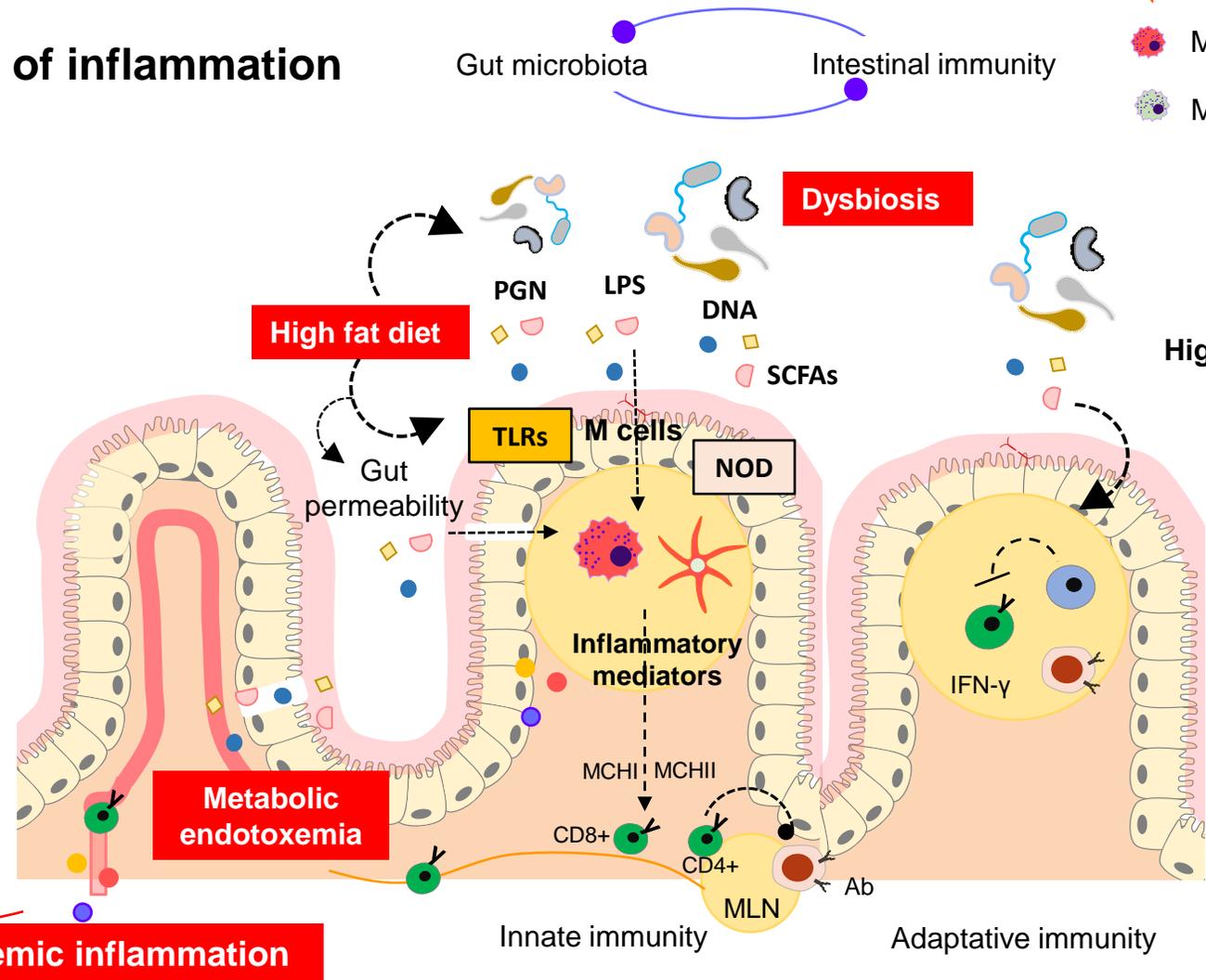
IL-6, TNF- α ,
IL-1 β
Leptin

Insulin resistance

Systemic Insulin resistance



Systemic inflammation



- DC
- T cells
- M1
- Treg
- M2
- B cells

High fat diet

Dysbiosis

High fat diet

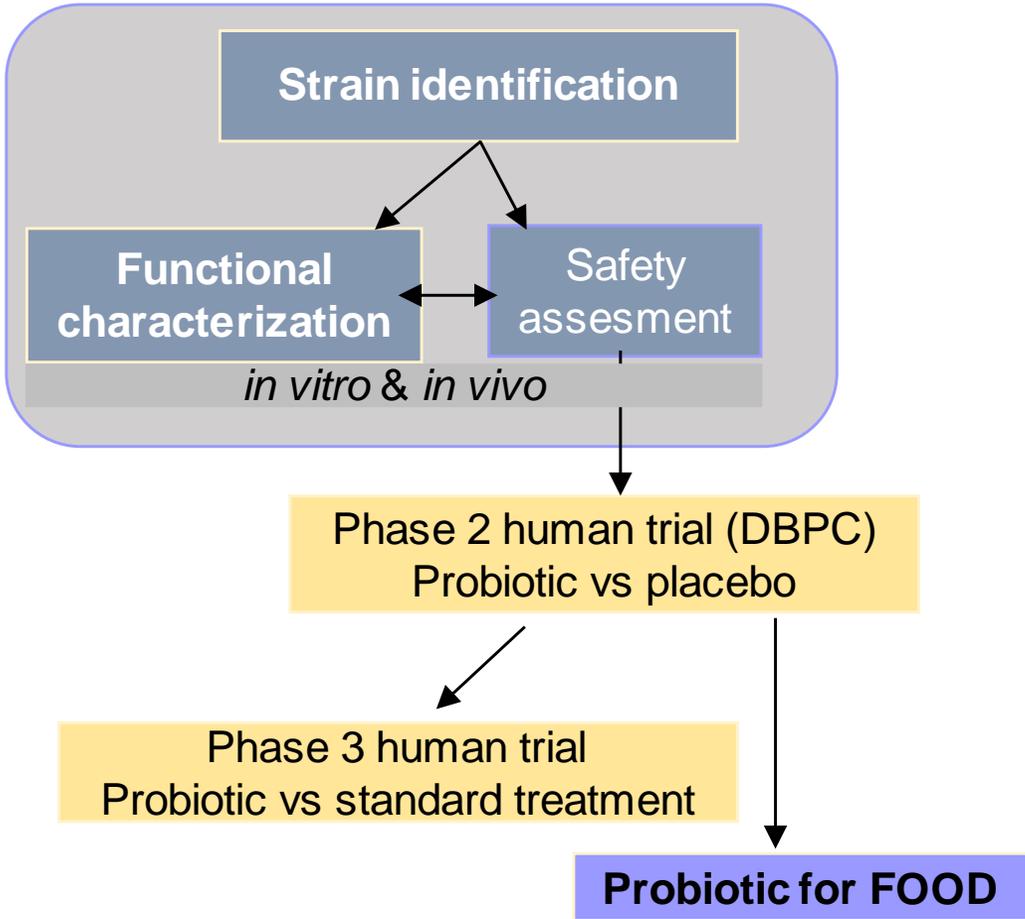
Metabolic endotoxemia

Innate immunity

Adaptative immunity



Evaluation of probiotics for food





Instituto de Agroquímica y Tecnología de Alimentos

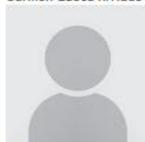
M. YOLANDA SANZ HERRANZ
CIENCIA DE ALIMENTOS
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ecología microbiana, nutrición y salud

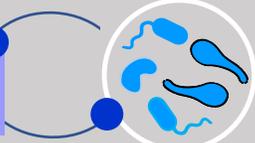


El grupo está abierto a cualquier tipo de colaboración con el entorno empresarial y académico en relación con estos temas.

Equipo

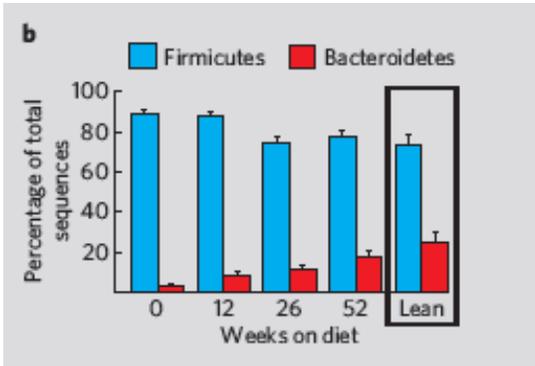
 Isabel Campillo Nuevo	 Carmen Laosa Arribas	 Victor Cerrudo Lopez
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 LORENA PERALES RIVAS	 Eva María Gómez del Pulgar Villanueva	 Marta Teresa Fernandez
 Inmaculada López Almela	 Maria Carmen Cenit Laguna	 Kevin Joseph Portune

Pathophysiology of metabolic and inflammatory diseases

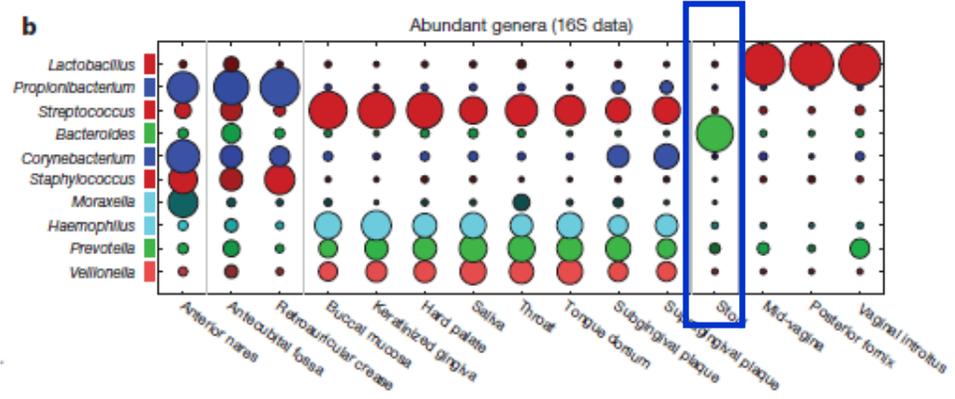




6.1 'On the way to evaluate new probiotics' *in vitro* functional characterization of *Bacteroides uniformis* CECT 7771



↑
Bacteroides-Prevotella
Bacteroides fragilis
Anti-obesity effects



In vitro Functional characterization

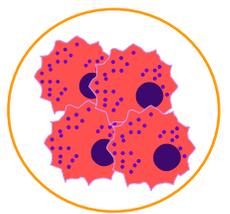


Strain identification

- Higher abundance in breast-fed than in formula-fed infants.
- ***B. uniformis* CECT 7771** isolated from stools of healthy breast-fed infants



Different strains of *Bacteroides*



Macrophages

Table 2. Effect of different *Bacteroides* strains on cytokine production by RAW264.7 macrophages.

<i>Bacteroides</i> strains	Cytokine production	
	TNF- α (pg/ml)	IL-10 (pg/ml)
DEMEN	491.2(112.1) ^{a, b'}	97.2(10.8) ^{a,a'}
LPS	1425.4(77.6) ^{b, a'}	162.3(37.6) ^{a,a'}
<i>B. dorei</i> SS1	3765.5(150.0) ^{b,b',a''}	215.8(12.5) ^{b,a',b''}
<i>B. ovatus</i> SU2	4515.7(211.3) ^{b,b',b''}	271.5(8.1) ^{b,b',b''}
<i>B. distasonis</i> CAY3	4462.4(173.9) ^{b,b',b''}	215.8(9.7) ^{b,a',b''}
<i>B. uniformis</i> CECT 7771	2998.4(50.4) ^{b,b',a''} ↓	341.3(13.5) ^{b,b',a''} ↑
<i>B. thetaiotaomicron</i> SAC4	2931.2(464.5) ^{b,b',a''}	109.2(3.0) ^{a,a',b''}
<i>B. fragilis</i> SX3	6657.3(278.3) ^{b,b',b''}	81.2(14.6) ^{a,a',b''}
<i>B. caccae</i> SV3	11622.0(818.3) ^{b,b',b''}	171.7(12.9) ^{b,a',b''}
<i>B. fingoldii</i> SX2	6535.8(62.2) ^{b,b',b''}	83.5(17.4) ^{a,a',b''}

6.1 'On the way to evaluate new probiotics' *in vivo* functional characterization of *Bacteroides uniformis* CECT 7771



In vivo Functional characterization of *Bacteroides uniformis* CE T 7771



DIET INDUCED OBESITY (DIO)

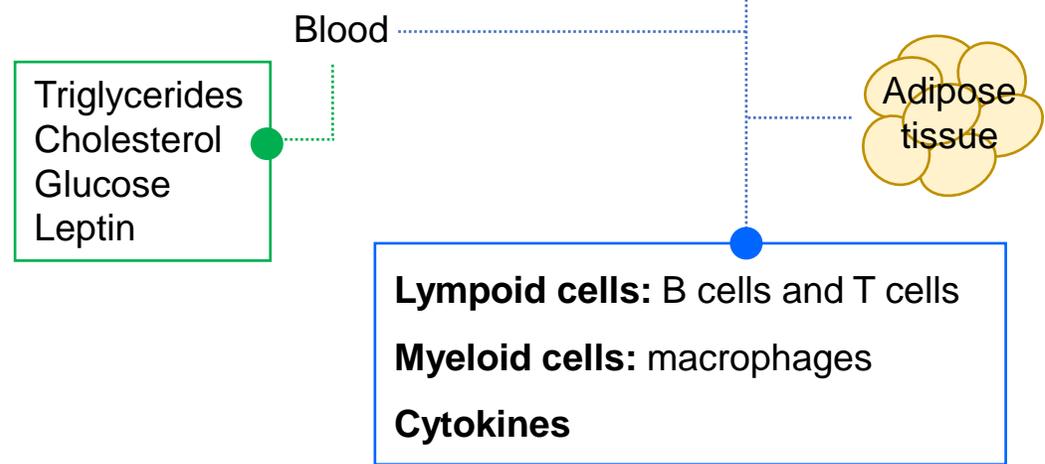
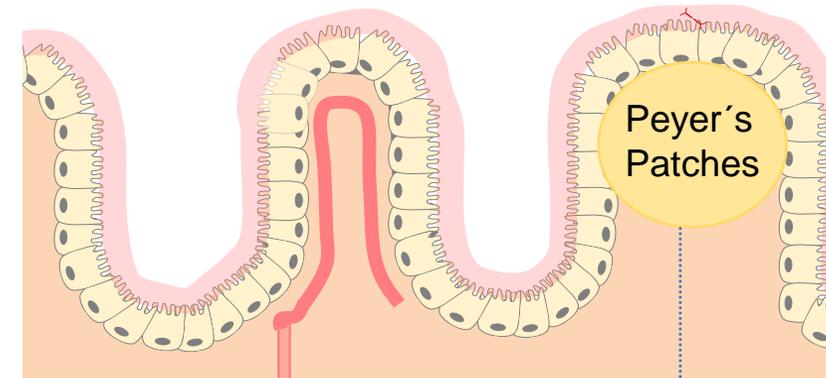


DIET	PROTEINS (% of Kcal)	CH (% of Kcal)	FAT (% of Kcal)	FRUCTOSE (% of Kcal)
SD	23	64	13 (corn oil)	0
HFHFD	18	34	48 (palm oil)	20



10 weeks: OGTT
 14 weeks: IMMUNOMETABOLIC PARAMETERS

IMMUNOMETABOLIC PARAMETERS



SD-Standard Diet
 HFHFD-High Fat High Fructose diet

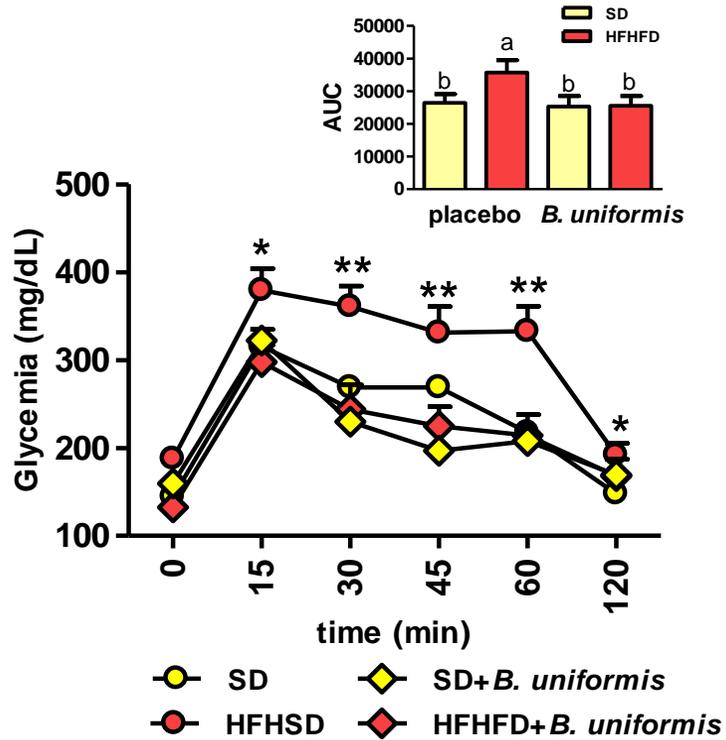
6.1 'On the way to evaluate new probiotics'

in vivo functional characterization of *Bacteroides uniformis* CECT 7771

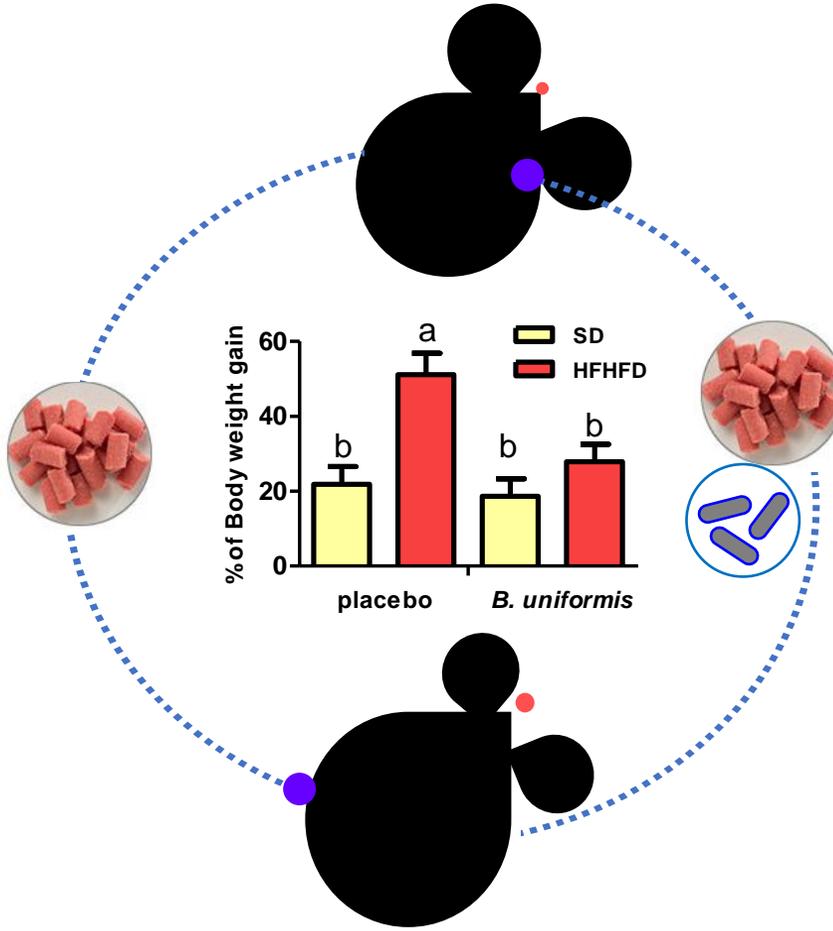


METABOLIC PHENOTYPE

Oral glucose intolerance

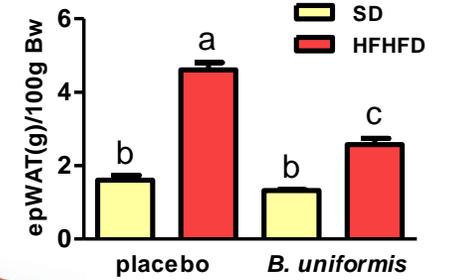
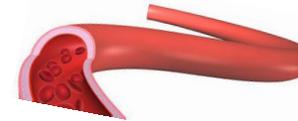
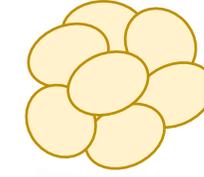


Lean phenotype

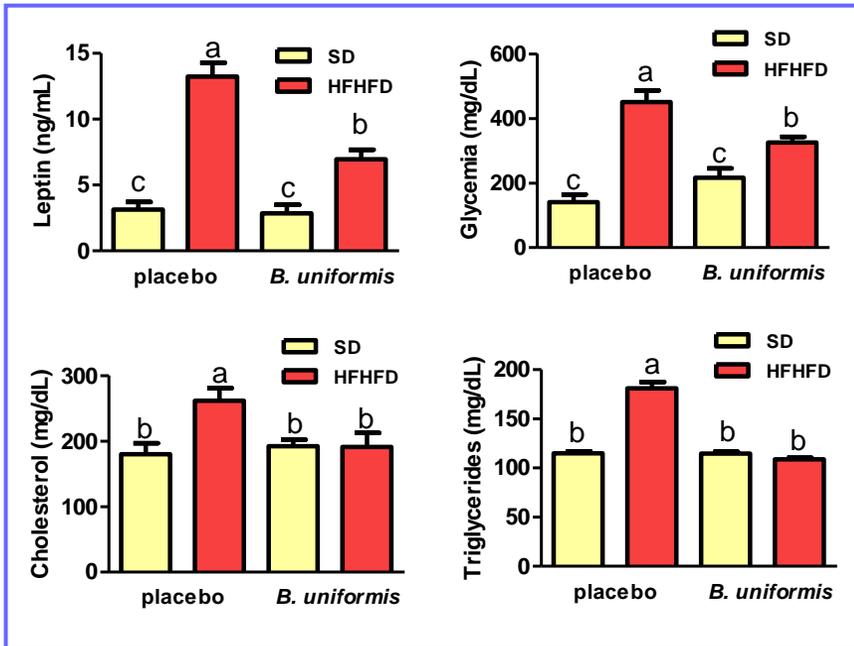


Obese phenotype

Adipose tissue



Hyperleptinemia, hyperglycemia, hypercholesterolemia, hypertriglyceridemia



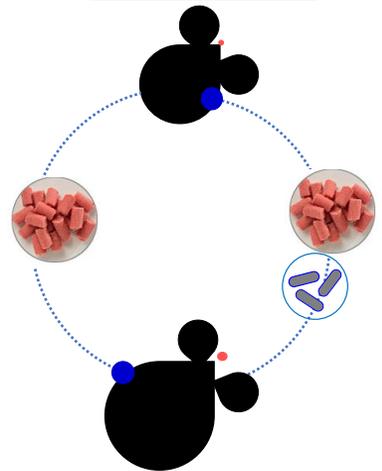
6.1 'On the way to evaluate new probiotics' in vivo functional characterization of *Bacteroides uniformis* CECT 7771



Mechanistic understanding of how *B. uniformis* promote anti-obesity effects

Lean phenotype

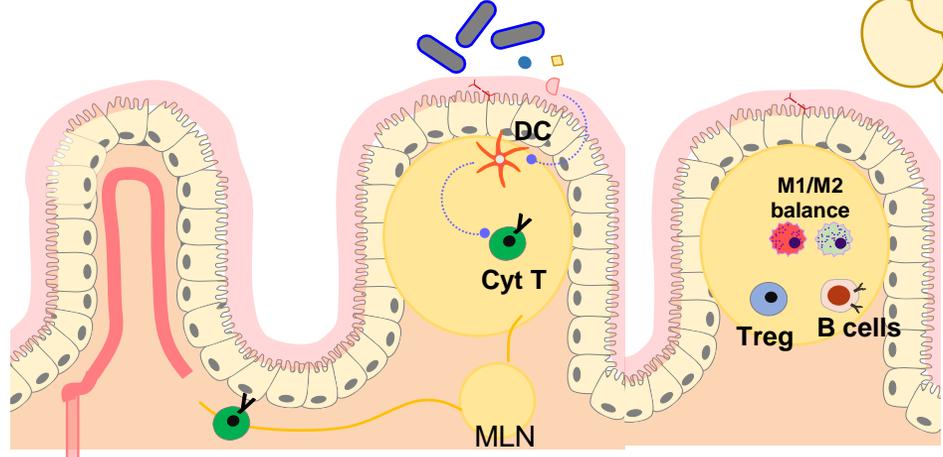
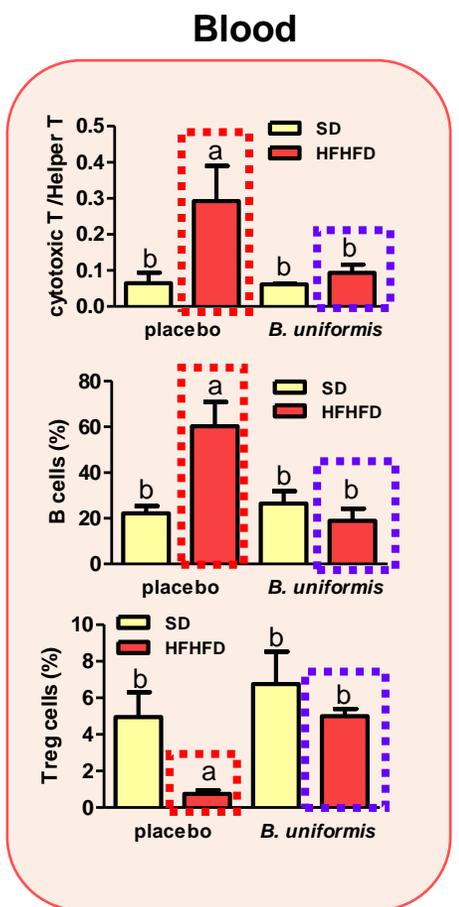
ANTIINFLAMMATORY RESPONSE



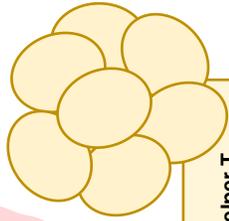
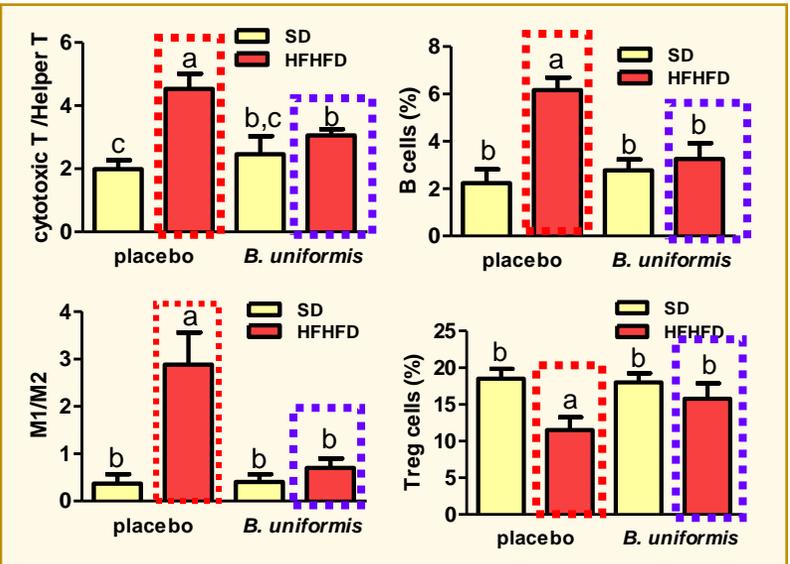
Obese phenotype

PROINFLAMMATORY STATE

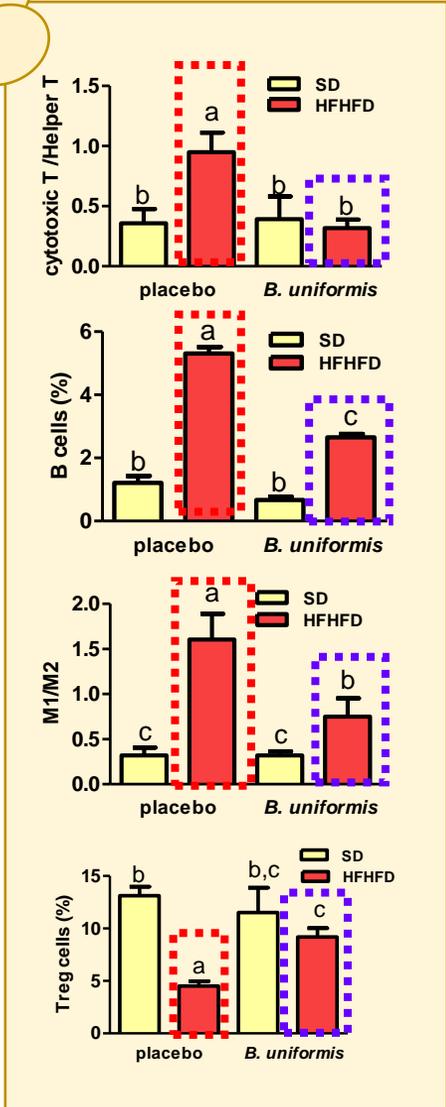
Dendritic cells (DC)
 Cytotoxic T cell (cyt T)
 regulatory T cells (Treg)



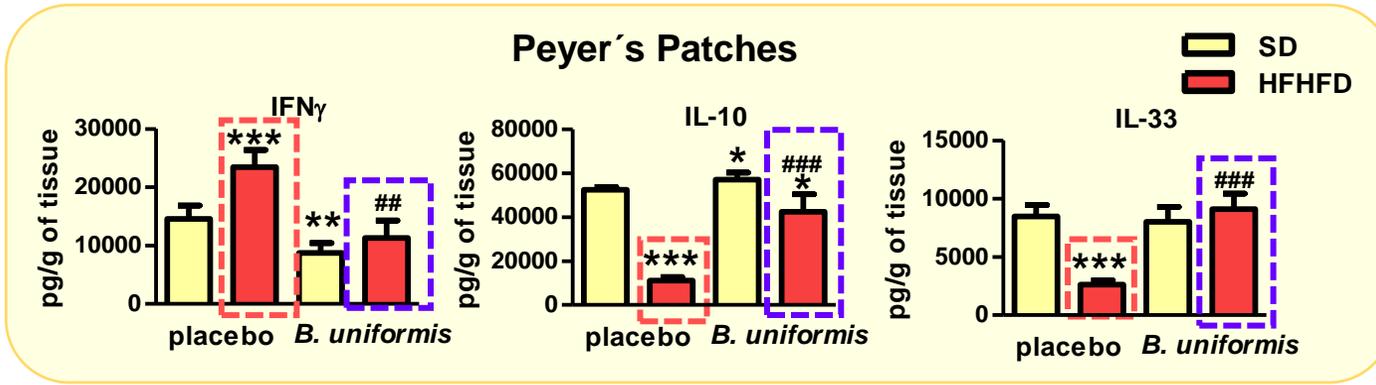
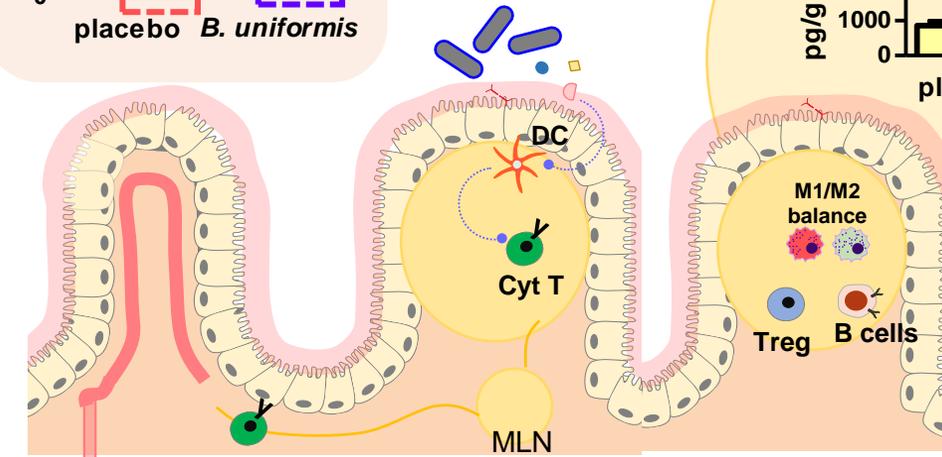
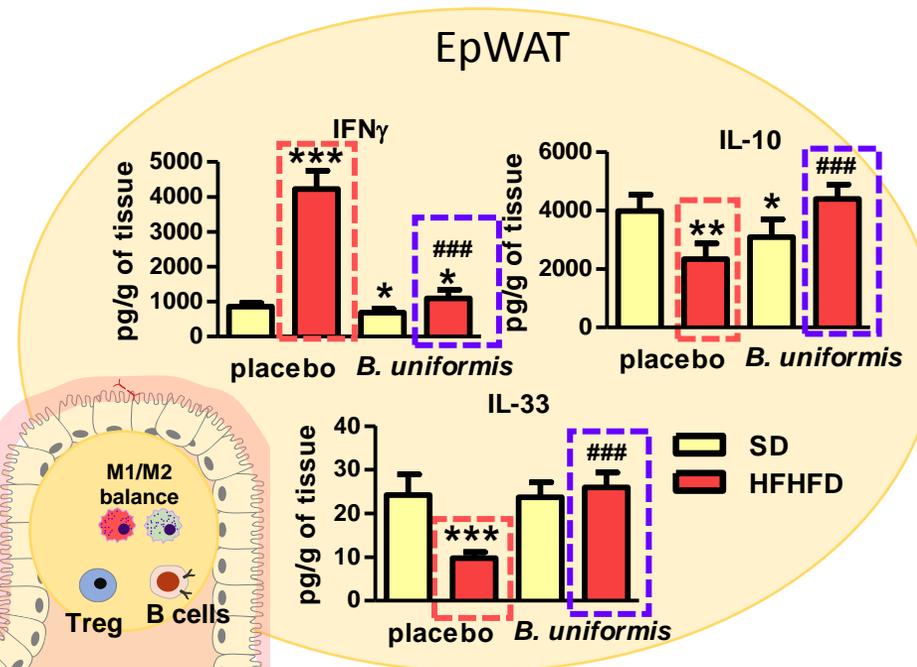
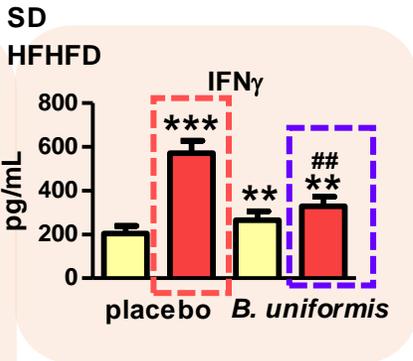
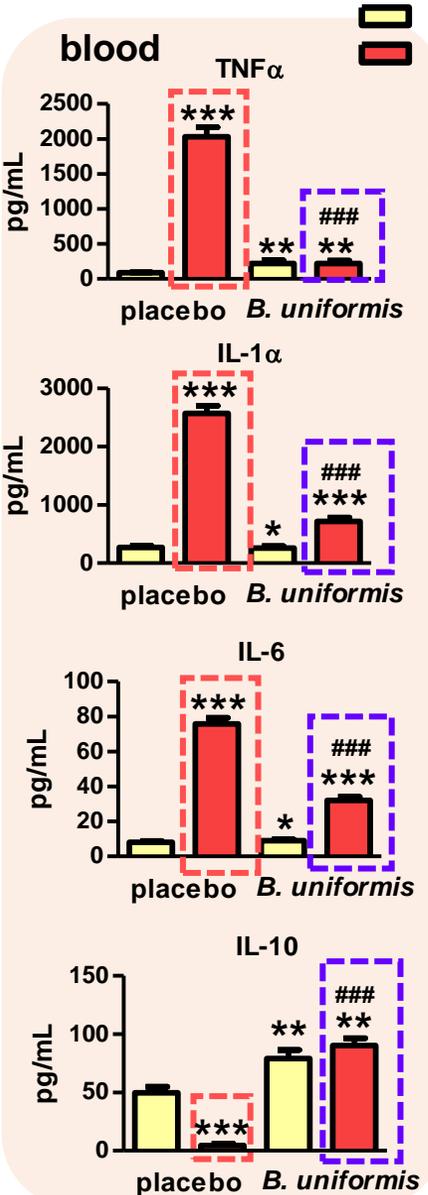
Peyer's Patches



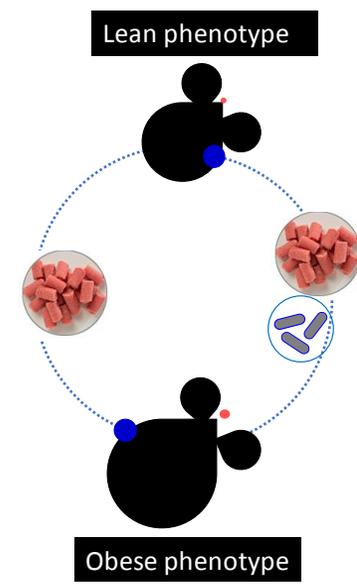
Adipose tissue



6.1 'On the way to evaluate new probiotics' in vivo functional characterization of *Bacteroides uniformis* CECT 7771



ANTIINFLAMMATORY STATE



PROINFLAMMATORY STATE

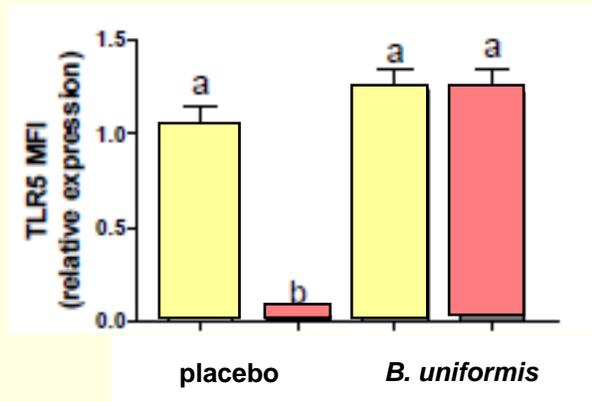
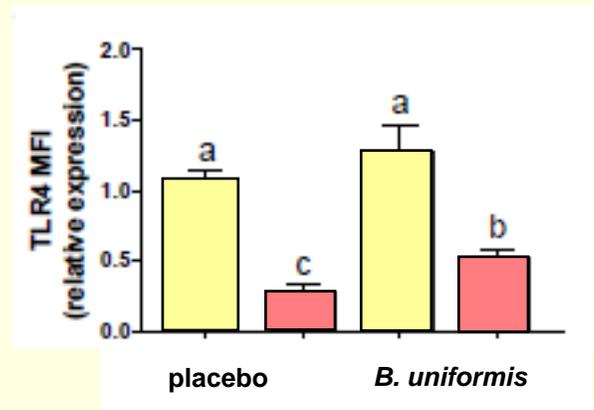
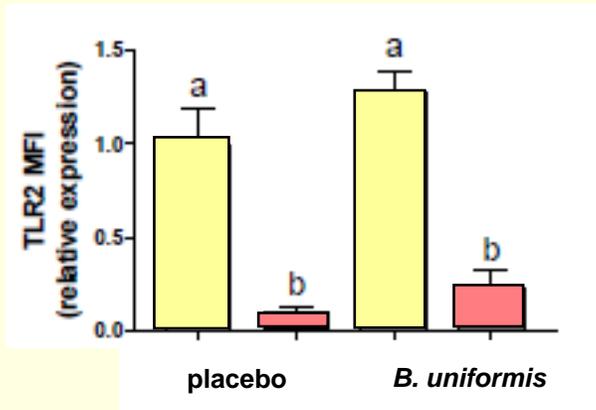
6.1 'On the way to evaluate new probiotics' *in vivo* functional characterization of *Bacteroides uniformis* CECT 7771



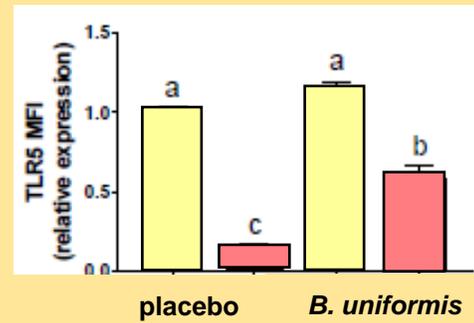
TLRs

ileum

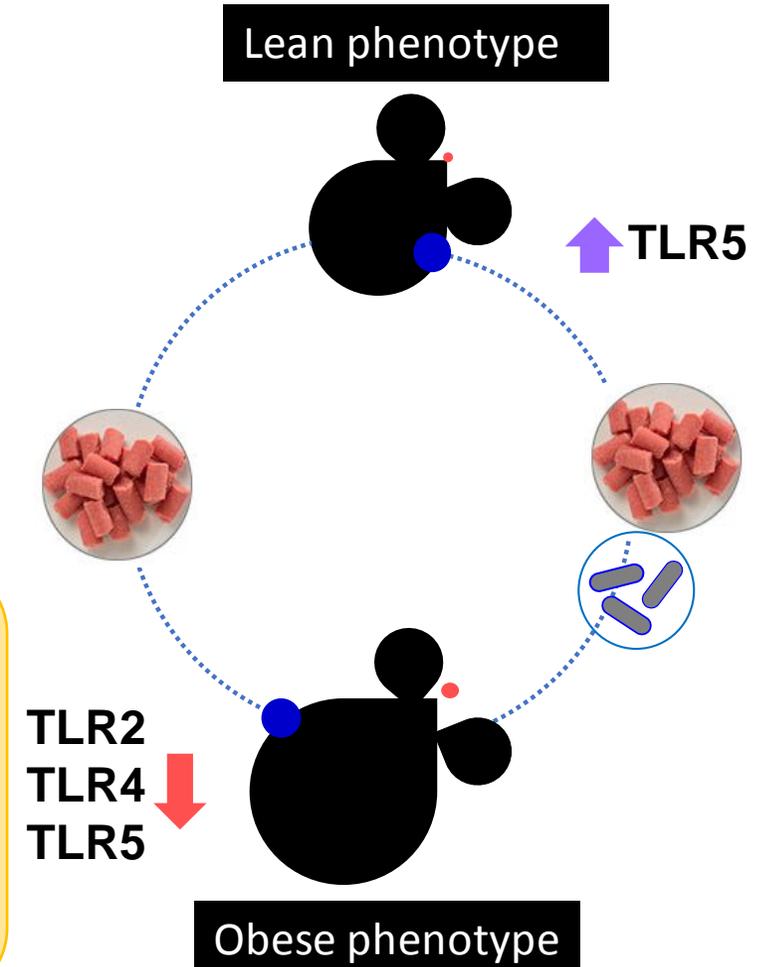
Peyer's Patches



Adipose tissue



SD
 HFHFD



6.1 'On the way to evaluate new probiotics'

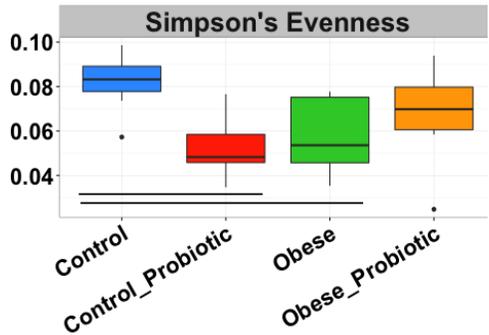
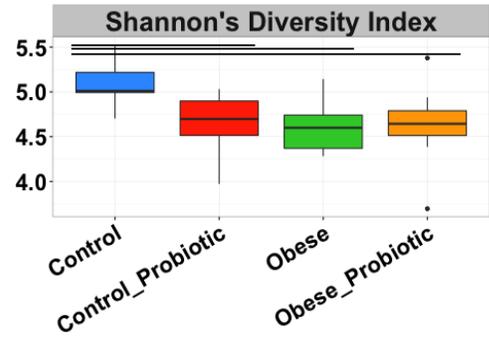
in vivo functional characterization of *Bacteroides uniformis* CECT 7771



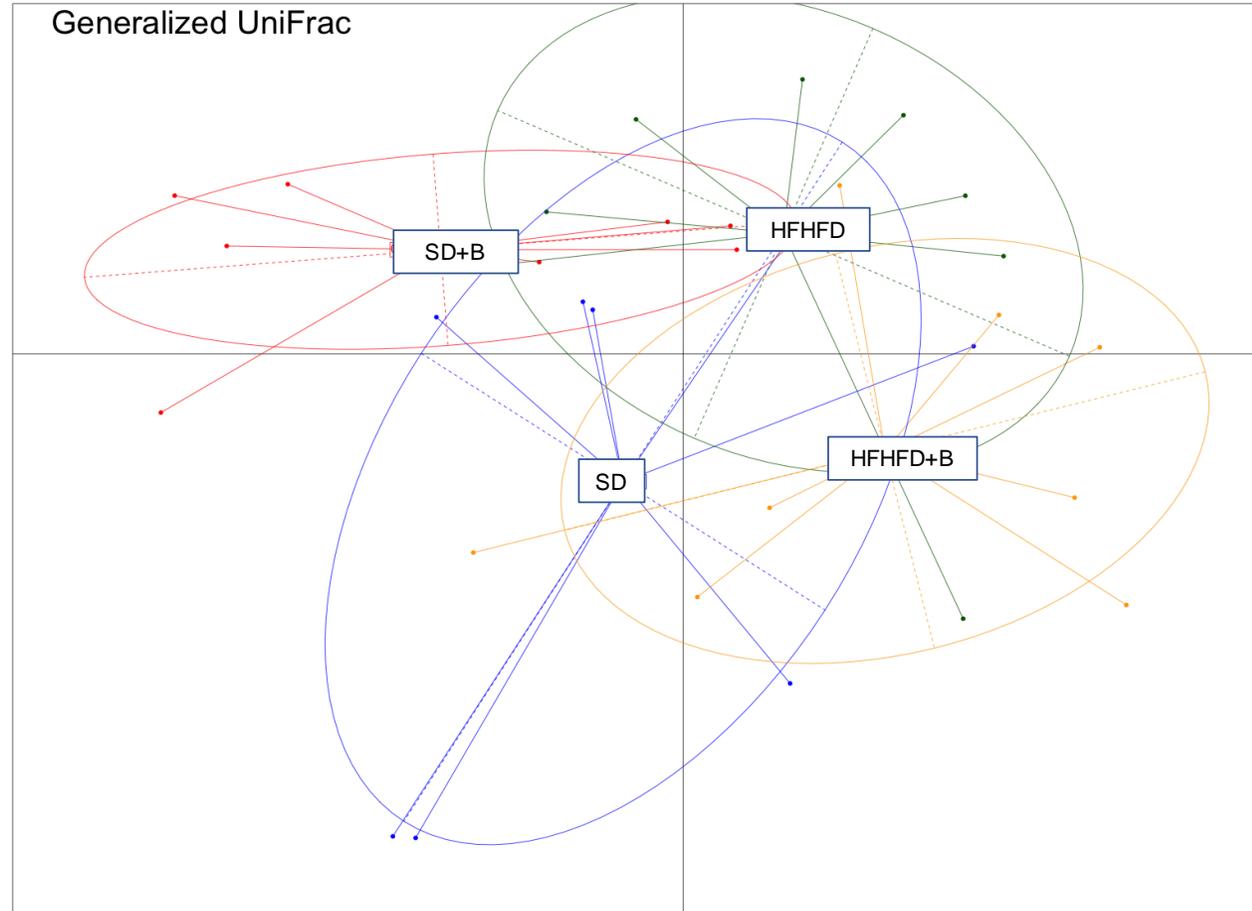
Gut microbiota

Kevin Joseph Portune

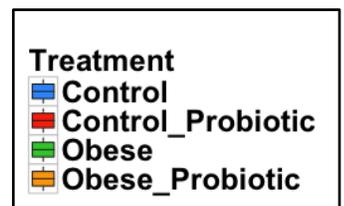
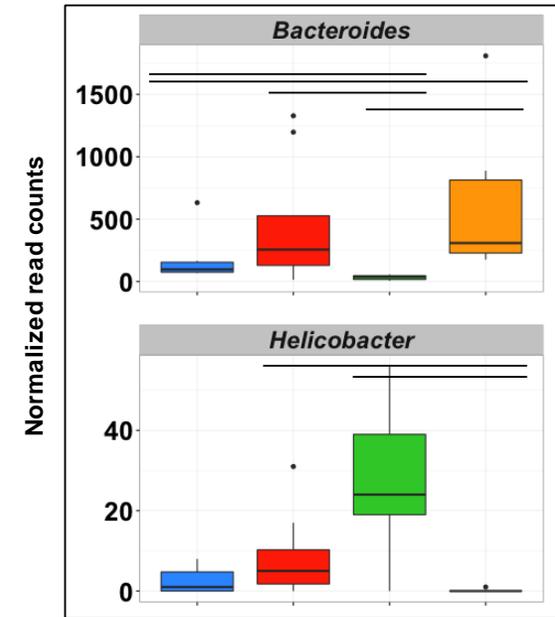
ALPHA DIVERSITY



BETA DIVERSITY



Genera



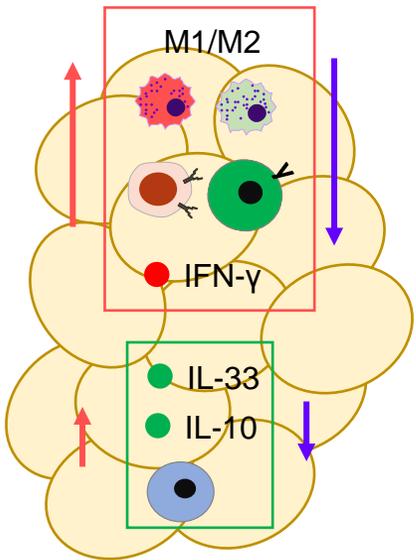
6.1 'On the way to evaluate new probiotics' *in vivo* functional characterization of *Bacteroides uniformis* CECT 7771



- DC
- M1
- M2
- T cells
- Treg
- B cells

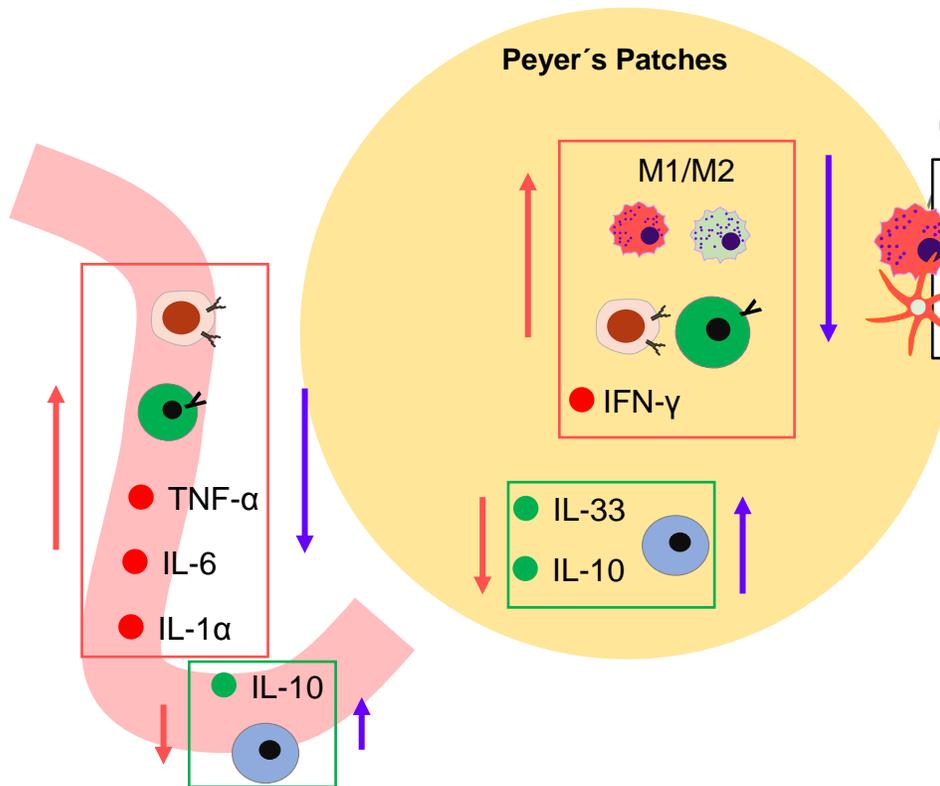
Summary

Pro-inflammatory state → Insulin resistance → obese-like phenotype
 Anti-inflammatory effects → Insulin sensitivity → lean-like phenotype

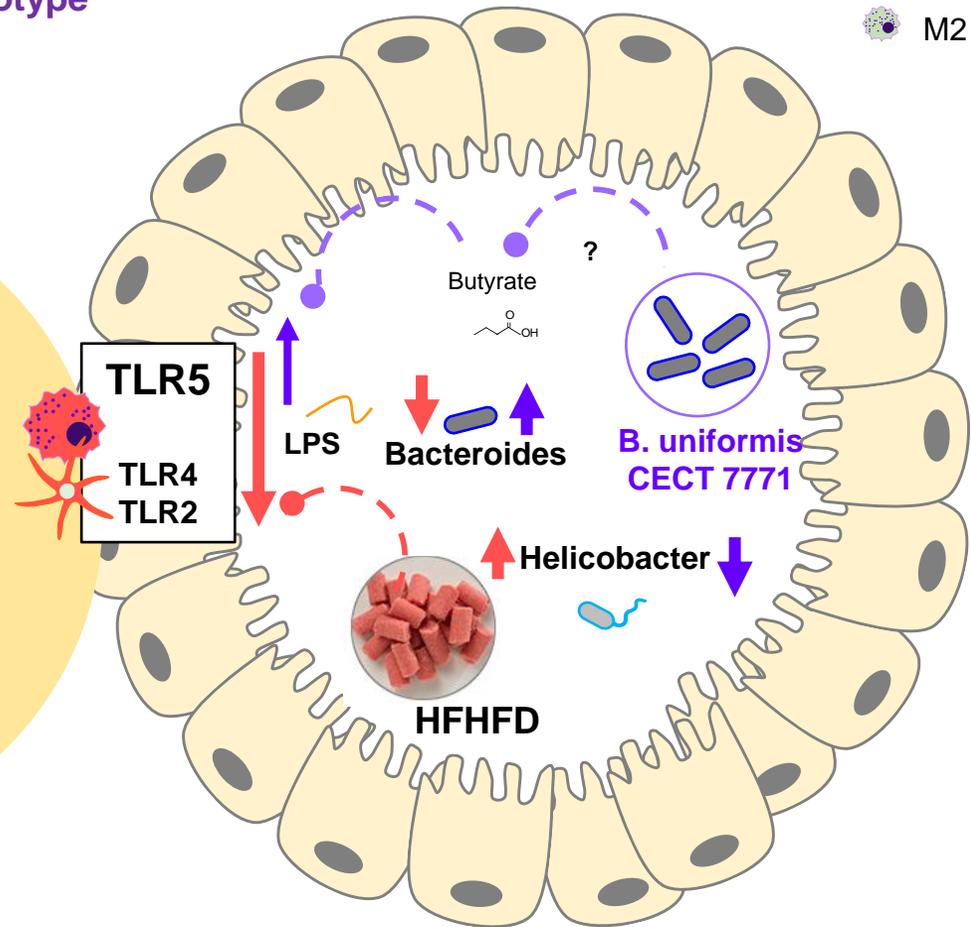


Adipose tissue

TLR5?



Peyer's Patches



T5KO mice → metabolic syndrome
 Vijay-Kumar et al. 2010

6.1 'On the way to evaluate new probiotics' in vivo safety assesment of *Bacteroides uniformis* CECT 7771



Safety assesment



Acute toxicity assay: 6 days



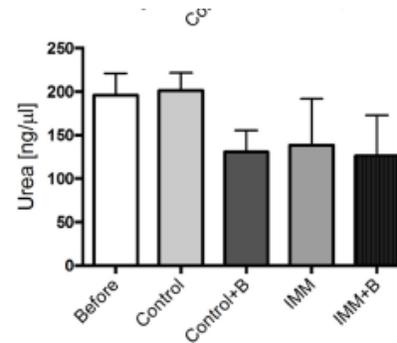
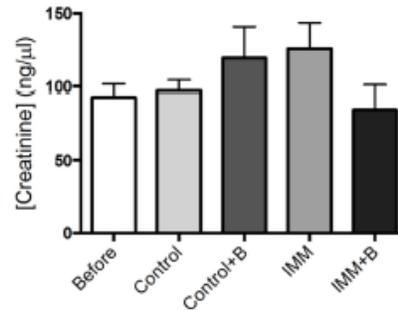
Placebo
 2x10⁹ CFU

Dose: 100 times higher than in humans

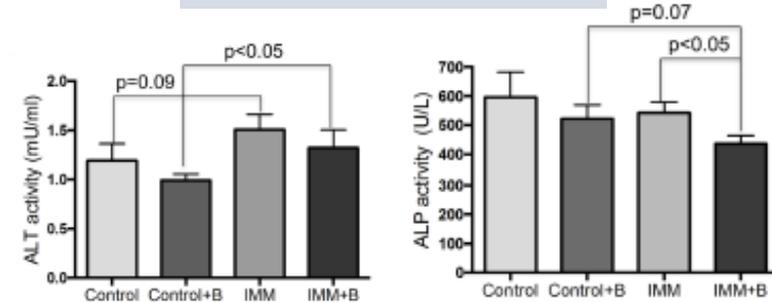
Immunocompetent mice
 Immunosuppressed mice

- Normal general health status: activity and behavior
- No difference in body weight gain or loss
- No bacterial translocation (blood, liver or mesenteric lymph nodes)

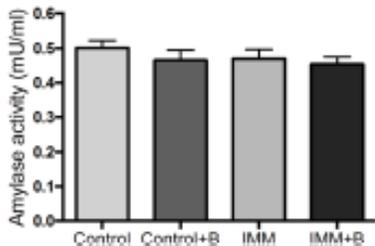
Normal kidney function



Normal liver function



Normal pancreatic function



Normal Gut mucosa integrity

Normal gut integrity
 Immunosuppression reduced:
 -globet cells and villus height/crypt depth ratio in jejunum.
 -crypt width in the colon.
 -*B. uniformis* CECT 7771 reversed the reduced height/crypt depth ratio in jejunum

Antiinflammatory response

B. uniformis CECT 7771 reduced pro-inflammatory cytokines
B. uniformis CECT 7771 restored inflammatory cytokines of immunosuppressed mice



Eva María Gómez del Pulgar Villanueva

Ongoing experiment

Chronic toxicity assay: 3 months



6.2 'On the way to evaluate new probiotics'

in vitro functional characterization of WBE and *B. uniformis* CECT 7771 intervention

Prebiotic & Probiotic intervention for FOOD

Functional characterization

in vitro

in vivo

Anti-obesity strategies

in vitro characterization of the dietary patterns and metabolic phenotypes of *B. uniformis* CECT 7771

The Glycolytic Versatility of *Bacteroides uniformis* CECT 7771 and Its Genome Response to Oligo and Polysaccharides

Alfonso Benítez-Páez^{1*}, Eva M. Gómez del Pulgar¹ and Yolanda Sanz



Bacteroides spp:
glycan enriched environments

Carbon source (0.5% w/v)

Glucose

inulin

Wheat Bran Extract (WBE)

gum arabic

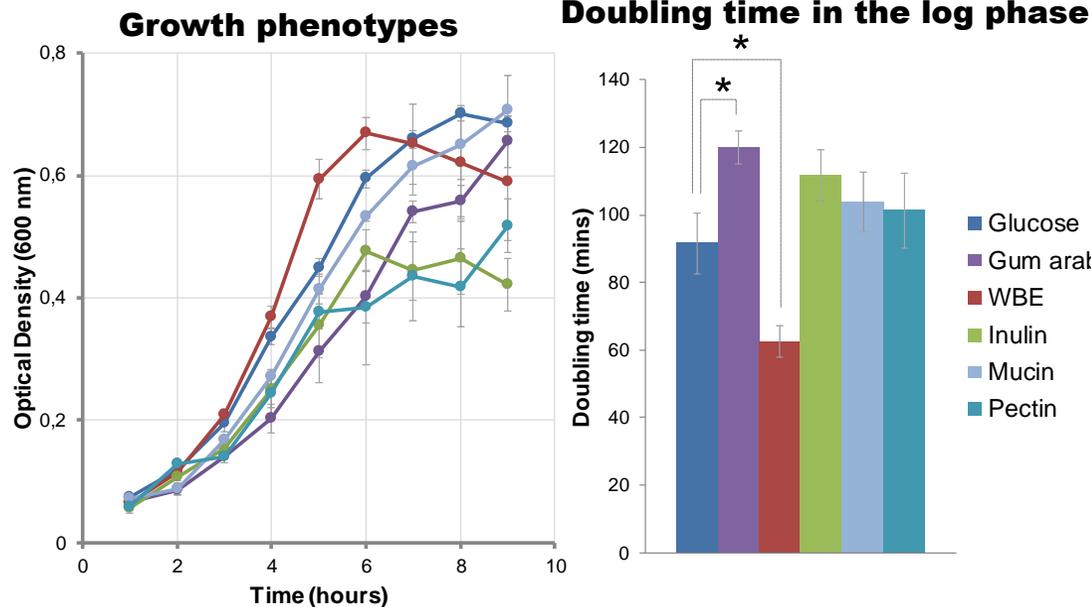
pectin

type II mucin



B. uniformis CECT 7771

Growth fitness of *B. uniformis* CECT 7771 in different dietary fibers



↑non-digestible carbohydrates:

Arabinoxylans

arabinoxylan-degrading enzymes



Arabinoxylan oligosaccharides (AXOS)



Metabolic health

SCFA (propionate)

6.2 'On the way to evaluate new probiotics'

in vivo functional characterization of WBE and *B. uniformis* CECT 7771 intervention



Prebiotic & Probiotic intervention for FOOD

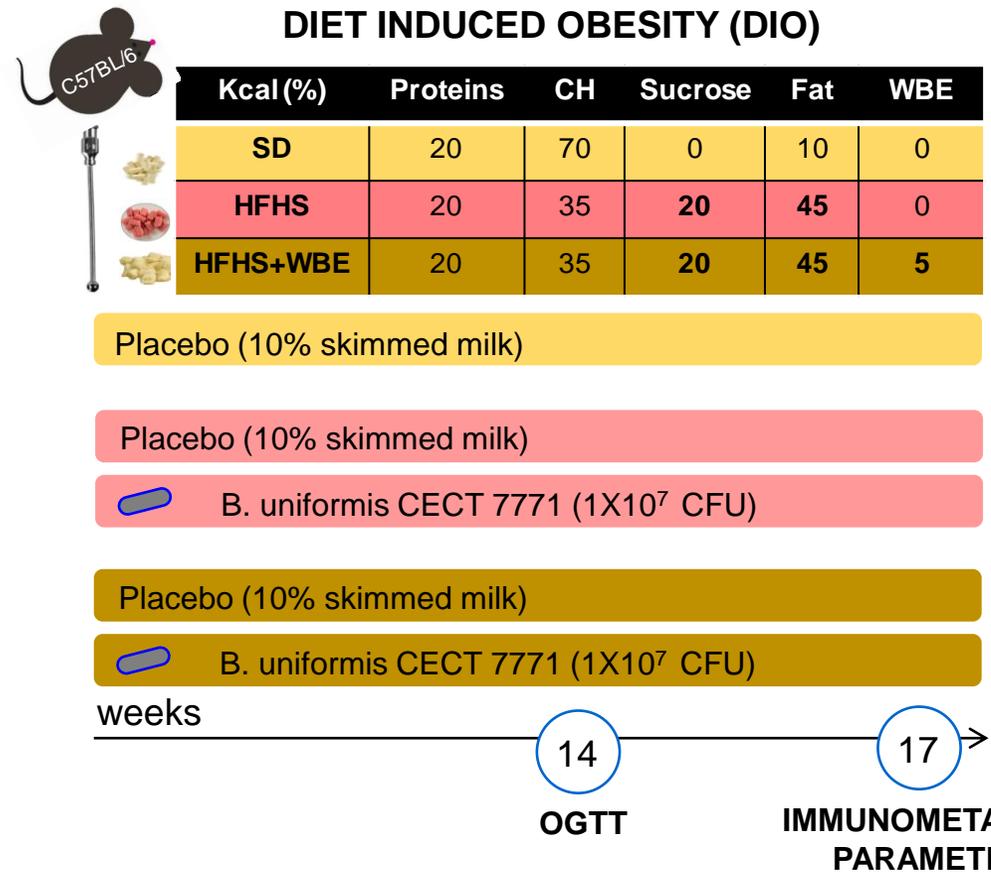
Anti-obesity strategies

Functional characterization

in vitro

in vivo

in vivo functional characterization on metabolic phenotype of WBE+*B. uniformis* CECT 7771 intervention



SD-Standard Diet

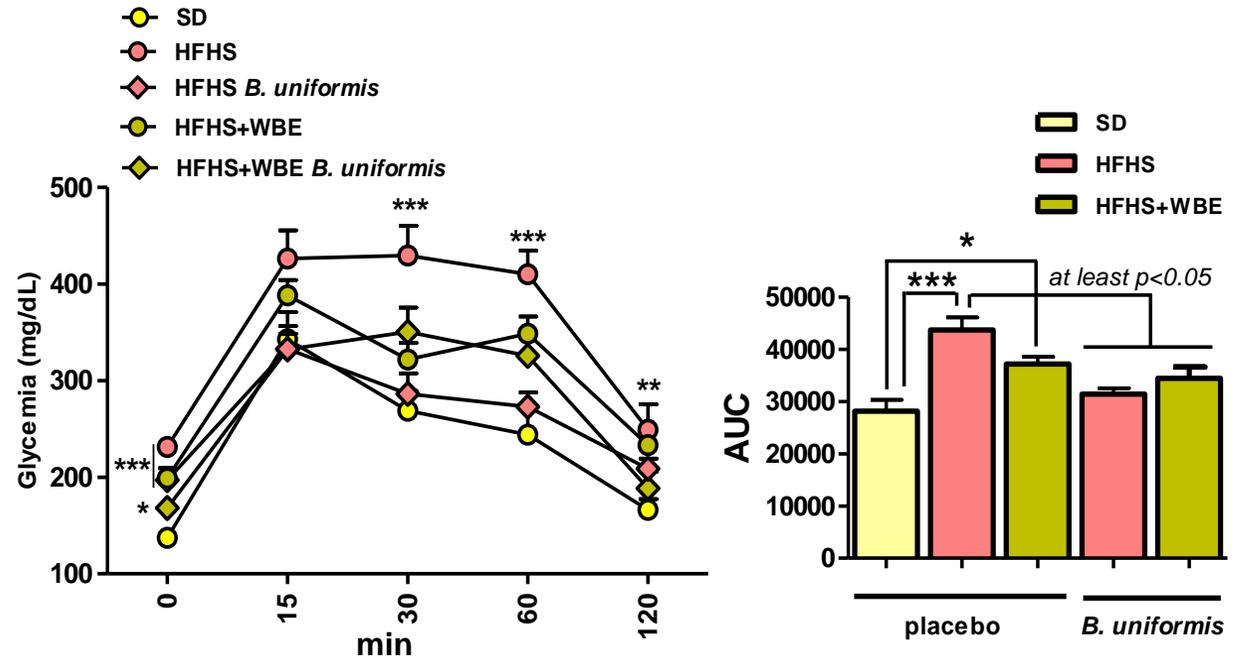
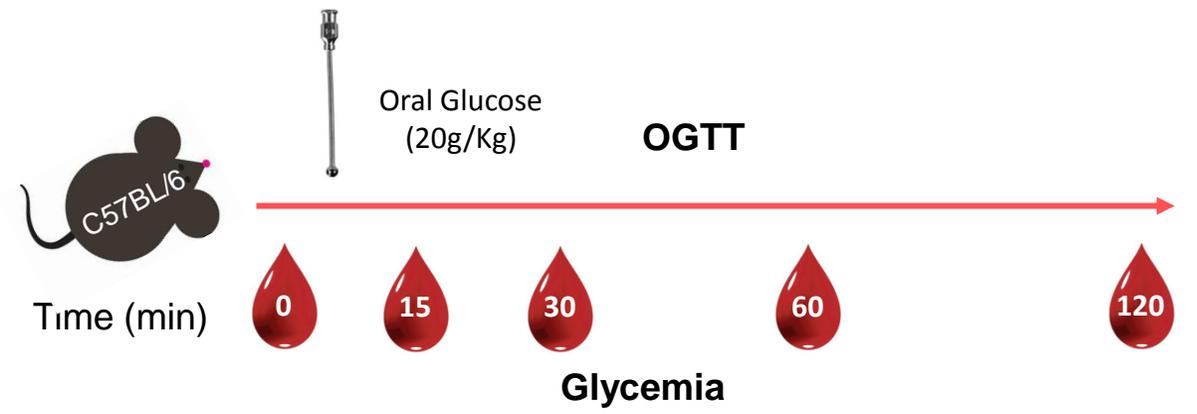
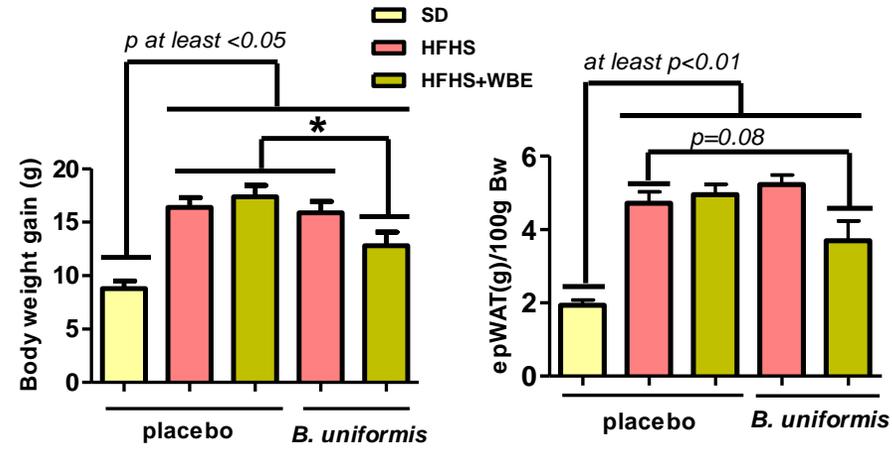
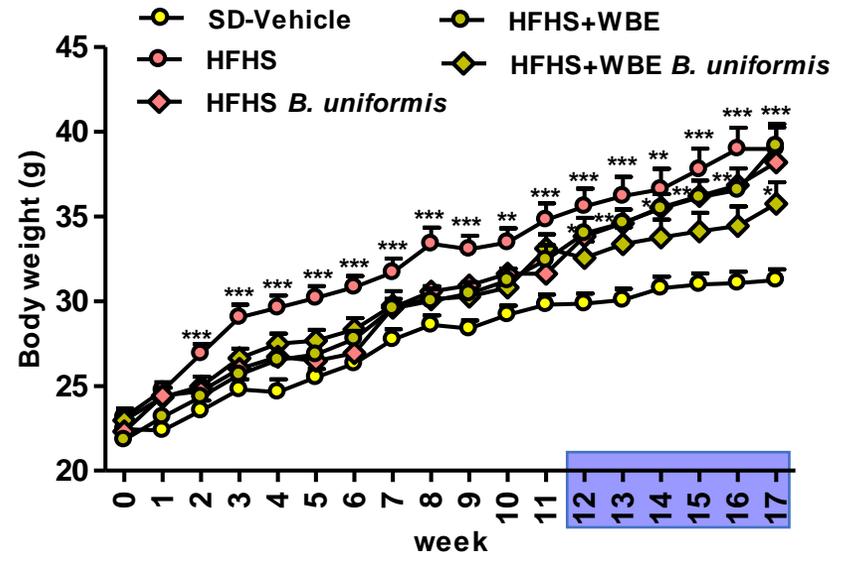
HFHS-High Fat High Sucrose diet

HFHS+WBE-HFHS+WBE



6.2 'On the way to evaluate new probiotics' *in vitro* functional characterization of WBE and *B. uniformis* CECT 7771 intervention

Preliminary results

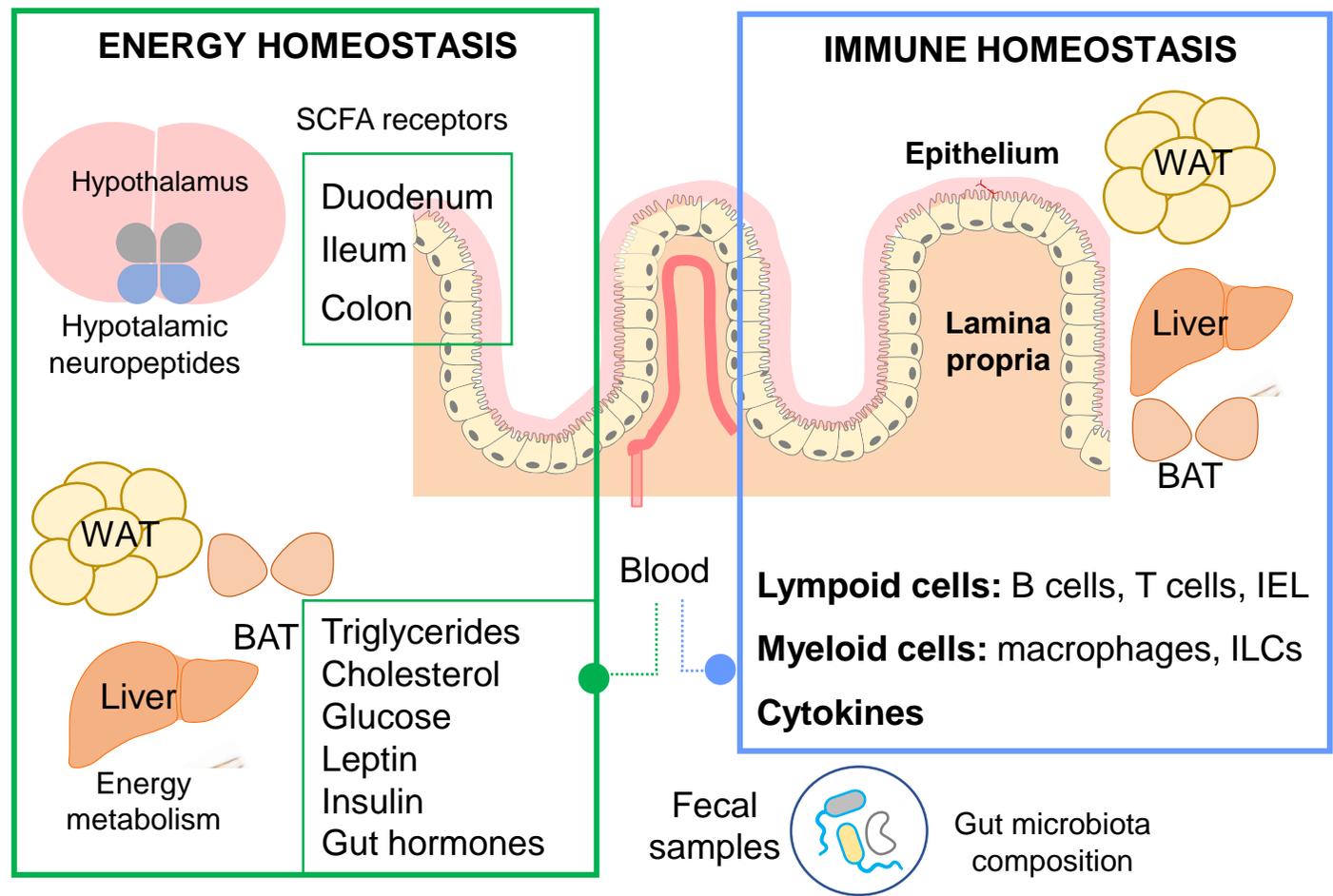




6.2 'On the way to evaluate new probiotics' *in vitro* functional characterization of WBE and *B. uniformis* CECT 7771 intervention

ONGOING EXPERIMENTS

IMMUNOMETABOLIC PARAMETERS



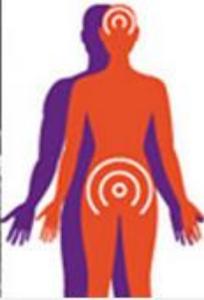


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y Tecnología de Alimentos



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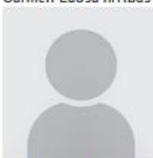
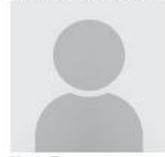
ecología microbiana, nutrición y salud

El grupo está abierto a cualquier tipo de colaboración con el entorno empresarial y académico en relación con estos temas.

**THANK YOU FOR YOUR
ATTENTION**

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