# CORRIERE DELLA SERA

Del lunedì · www.corriere.it

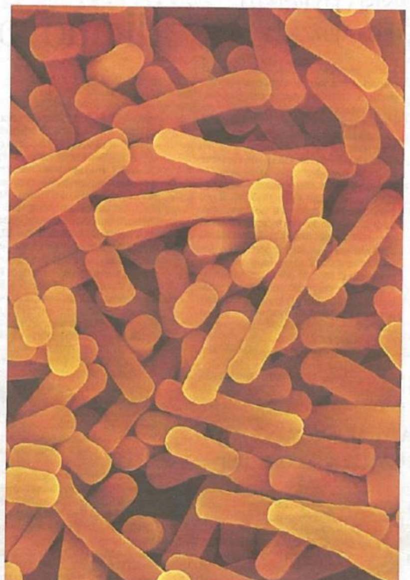
## Lunedì 27/1/2014

**La scoperta** Uno studio californiano prova che lo stato dell'intestino influisce direttamente sul cervello

# Domani i microbi ci salveranno

## Gli organismi microscopici possono combattere le malattie

di MASSIMO PIATTELLI PALMARINI



**Effetti positivi**
Progressi nel comportamento, maggiore resistenza allo stress, minori sintomi di ansia, una accentuata sensibilità

Il ***microbiota*** è arrivato sui mass media ...

## Domenica 26/1/2014

medicina pratica

**Mi spieghi dottore** Come ci si accorge di avere il **diabete di tipo 2**?

**Lo specialista**

# Una malattia silente per anni, che si scopre con gli esami

di ANTONELLA SPARVOLI

Antonio Ceriello

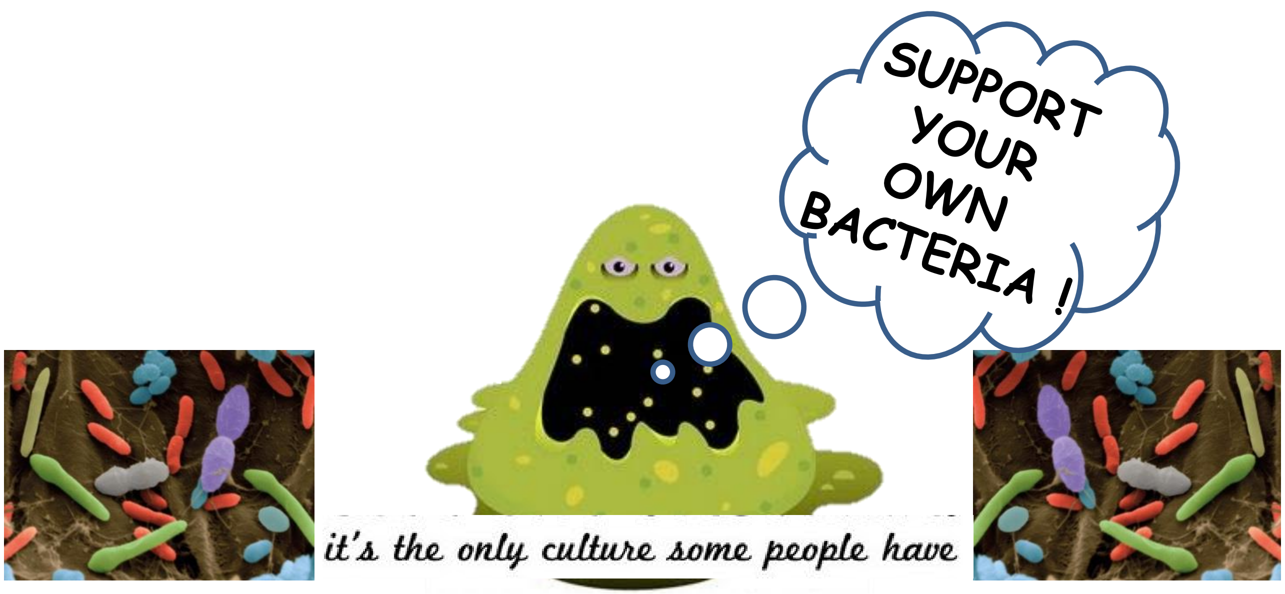
Talvolta la l'unico segnale è l'aumento della tendenza a urinare. Altrimenti è il test della glicemia a svelare la malattia

...ma la ***CHIRURGIA***

***NO !***

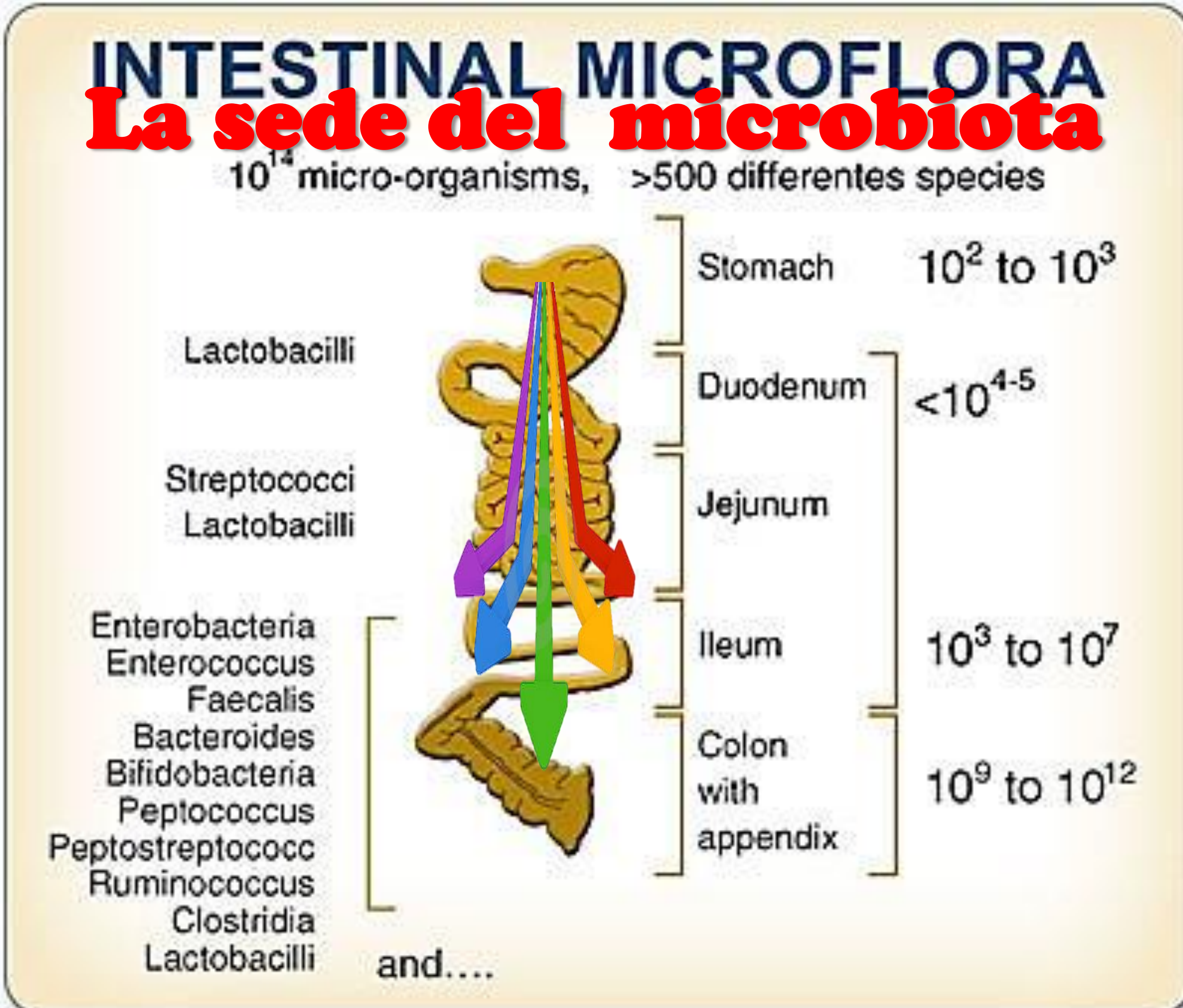
# Microbiota e chirurgia metabolica: una nuova frontiera

Nicola Basso
Padova 7-8 marzo 2014



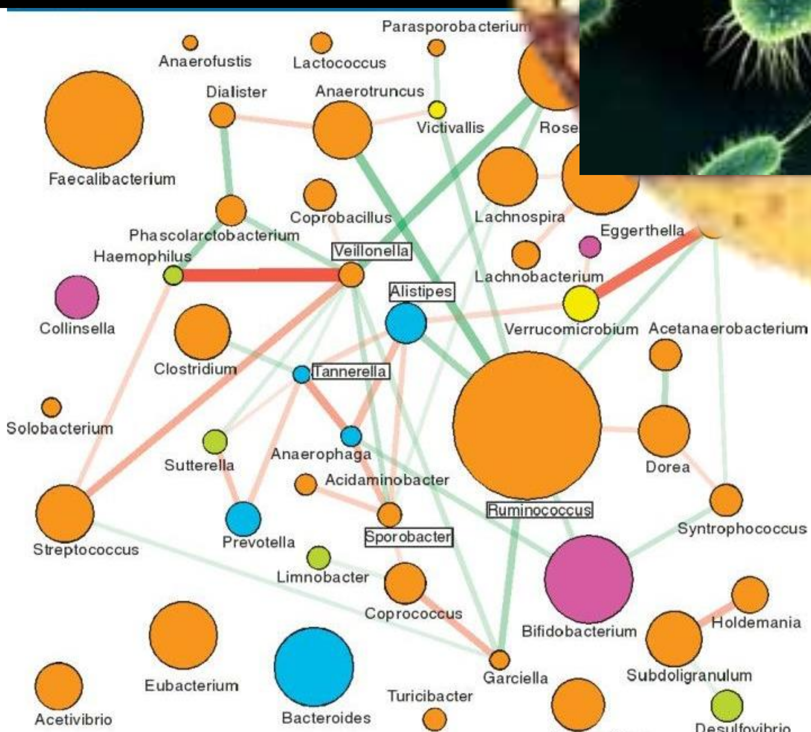
# L'organo microbiota

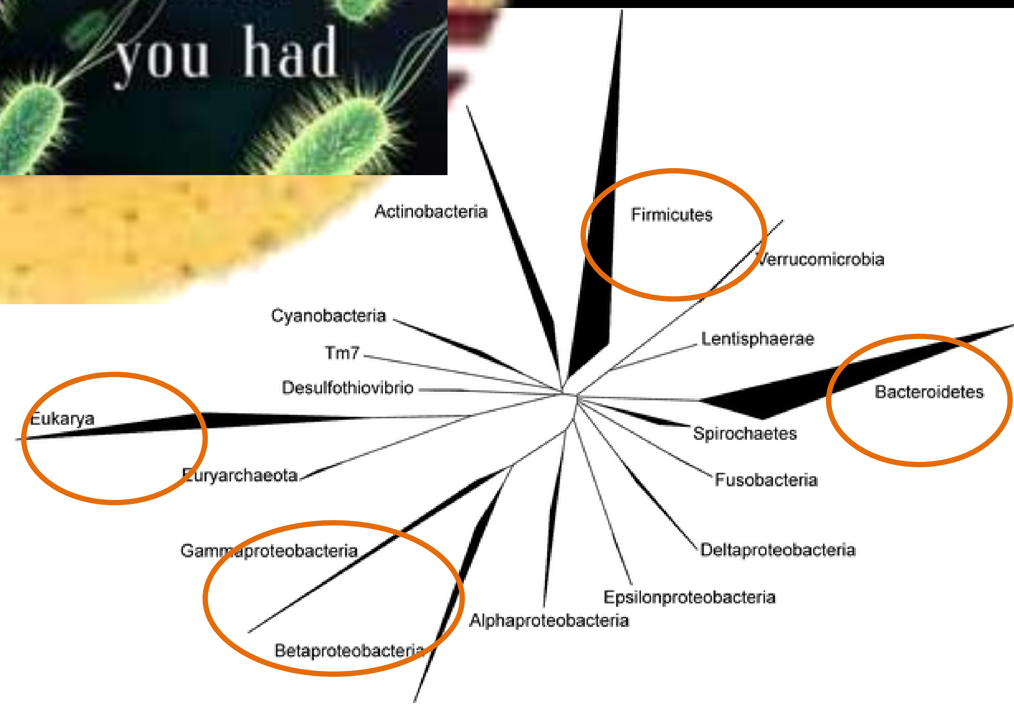
# La sede del microbiota




Increasing numbers and diversity of microbiota

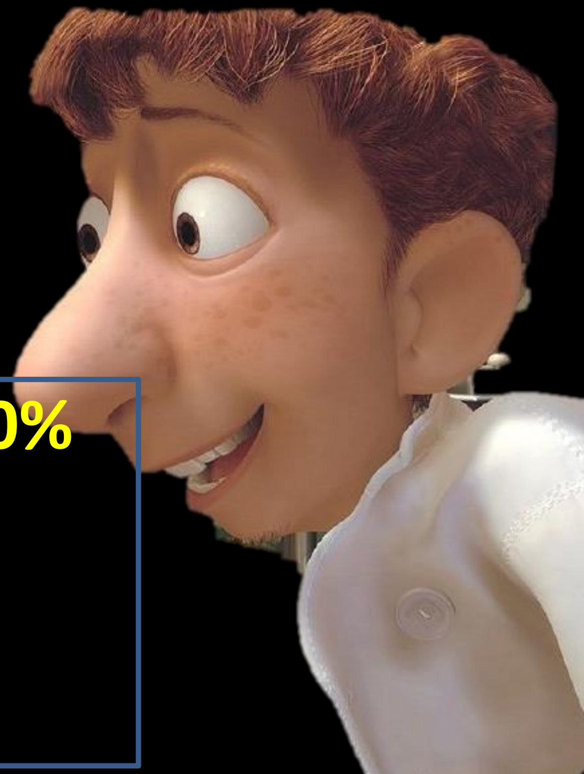
# Diversity of microbiota

# Microbiota

## in topo e uomo

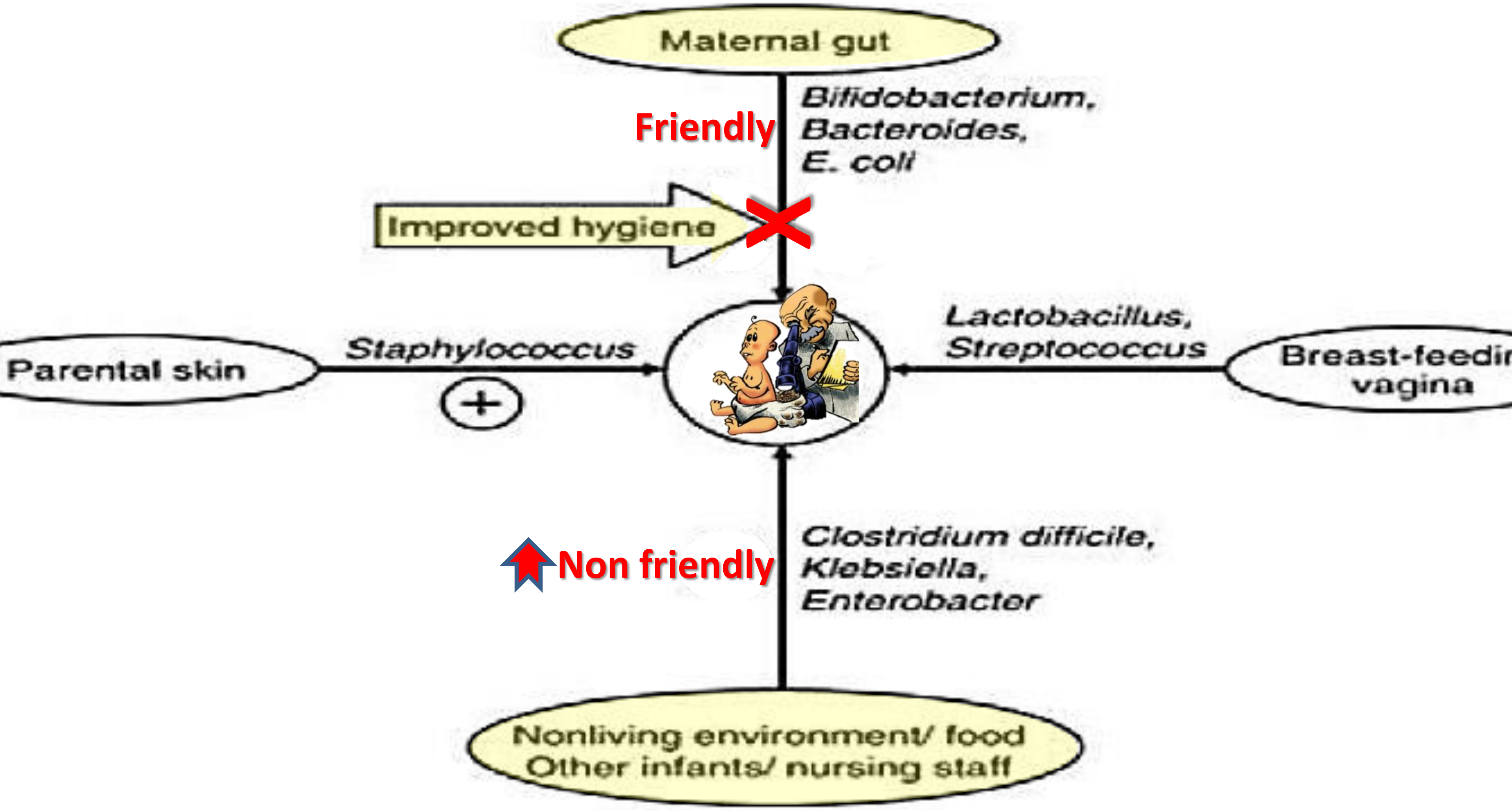


| | | |
|---|---|---|
| **Gram+** | **Firmicutes** | **60-80%** |
| | Actinobatteri | |
| **Gram-** | **Bacteroidetes** | **20%** |
| | Proteobacteria | |

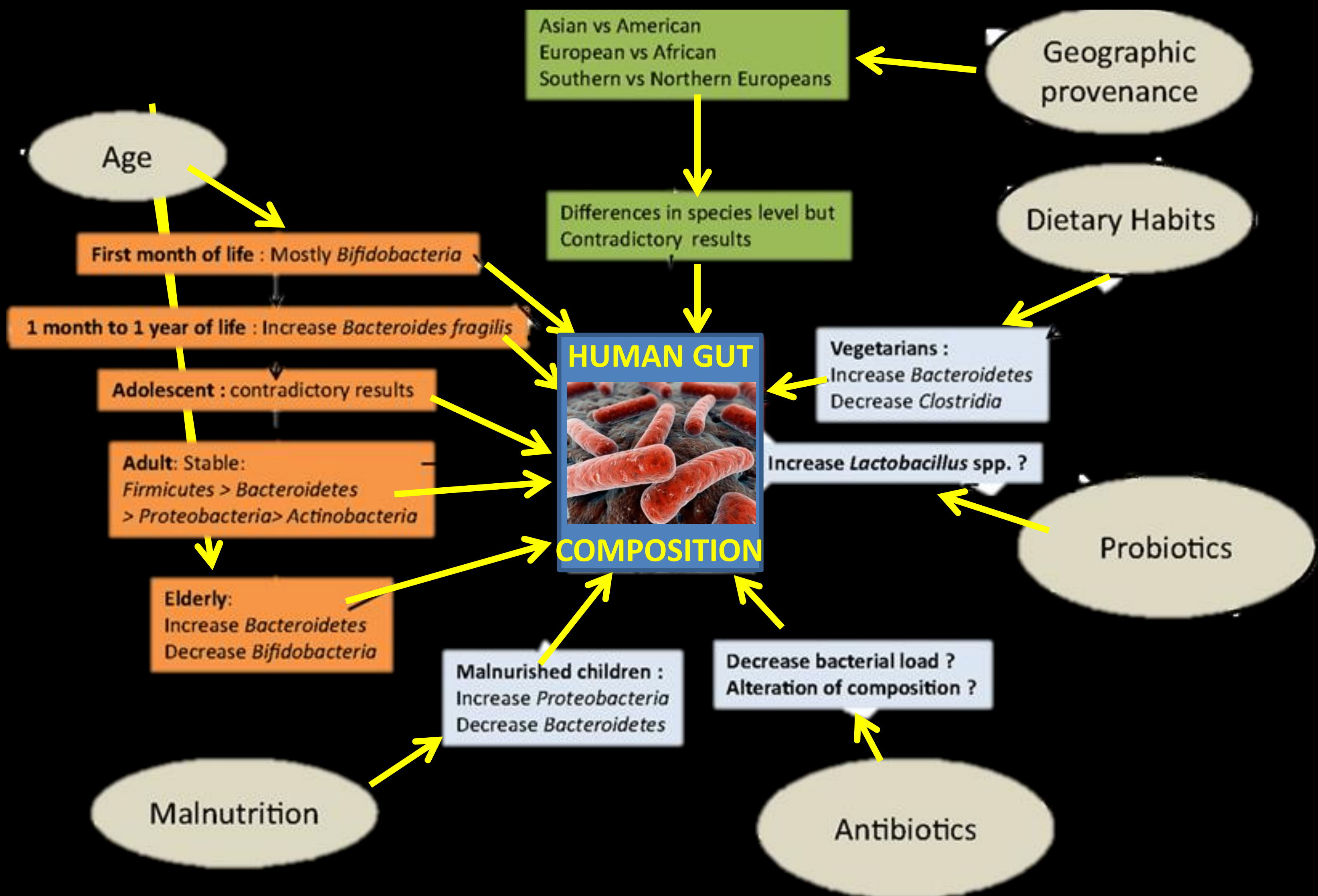

Microbiota:
ce ne sono tanti

# MICROBIOTA COMPOSITION

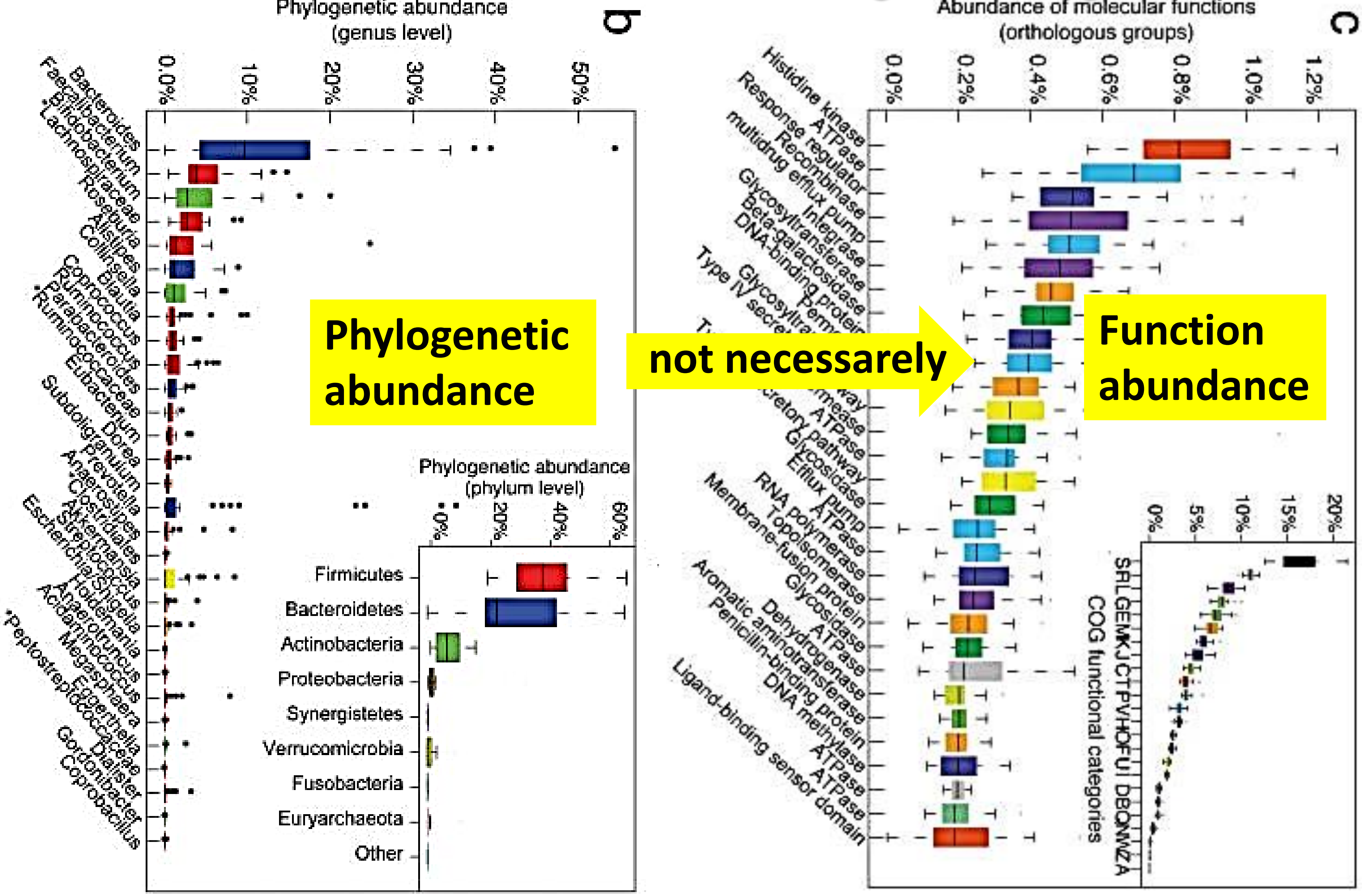
# Initial Colonization



# MICROBIOTA COMPOSITION



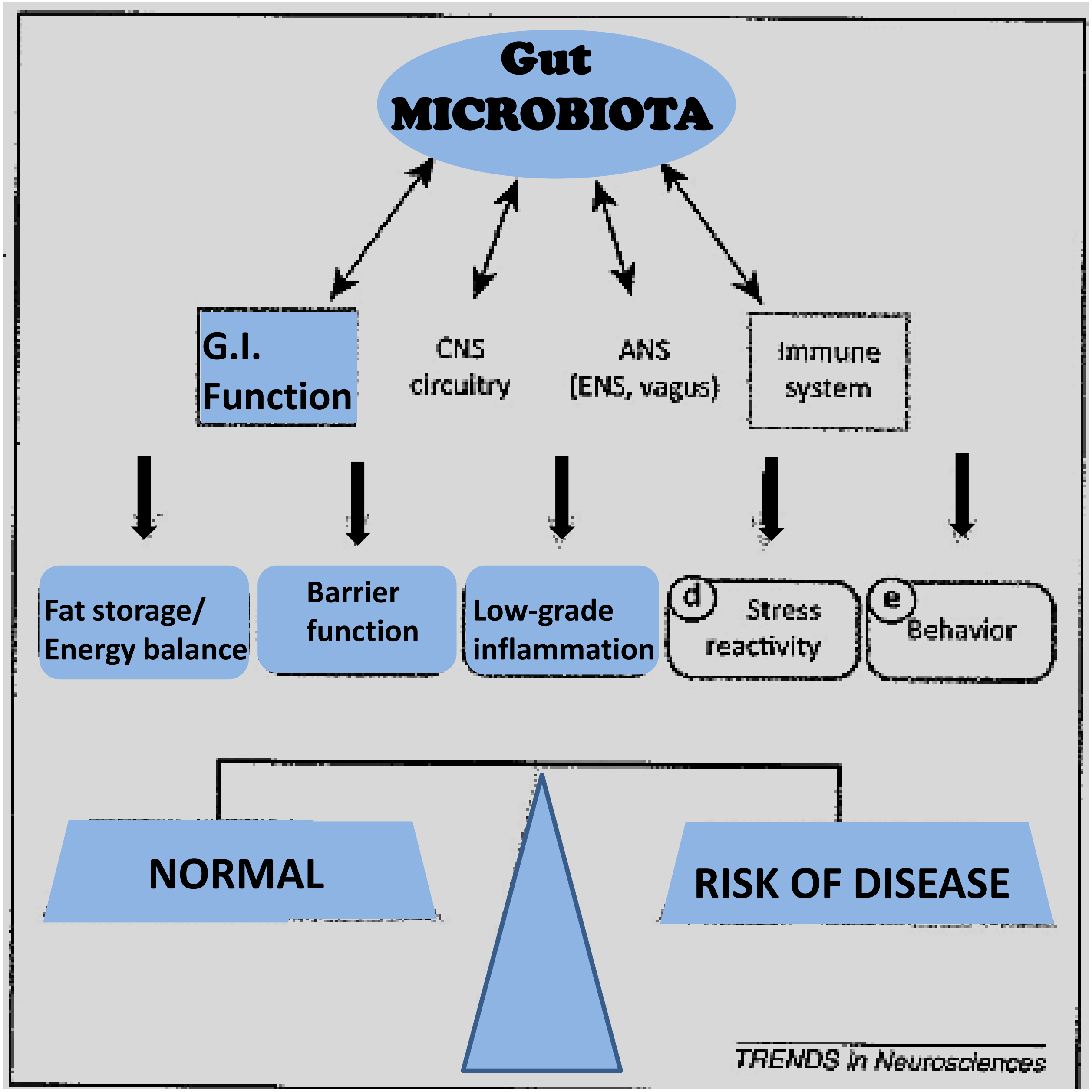
# -Functional diversity analysis-




Abundant molecular functions not necessarely provided by abundant species.

Arumugam M 2011

# Microbiota: funzioni multiformi.




**Bidirectional communication between gut microbiota and gut-brain axis influences homeostasis…**

**…leading to alterations in fat storage, energy balance, barrier function, low grade inflammation**

**Figure 1.** Bidirectional communication between gut microbiota and components of the gut–brain axis influence normal homeostasis and may contribute to risk of disease. Alterations in gastrointestinal (GI), central nervous system (CNS), autonomic nervous system (ANS), and immune systems by microbiota may lead to alterations in **(a)** fat storage and energy balance; **(b)** GI barrier function; **(c)** general low-grade inflammation (GI and systemic); **(d)** increased stress reactivity; and **(e)** increased anxiety and depressive-like behaviors. Each of these mechanisms is implicated in the pathophysiology of mood and anxiety disorders. Abbreviation: ENS, enteric nervous system.

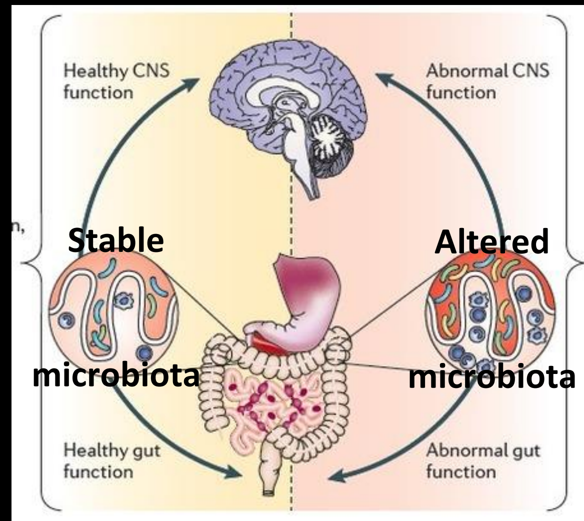
Foster J.A. ,2013

# Gut–brain axis: how the microbiome influences anxiety and depression

**Germ-free mice were more active, less anxious and less risk-averse than usual.**

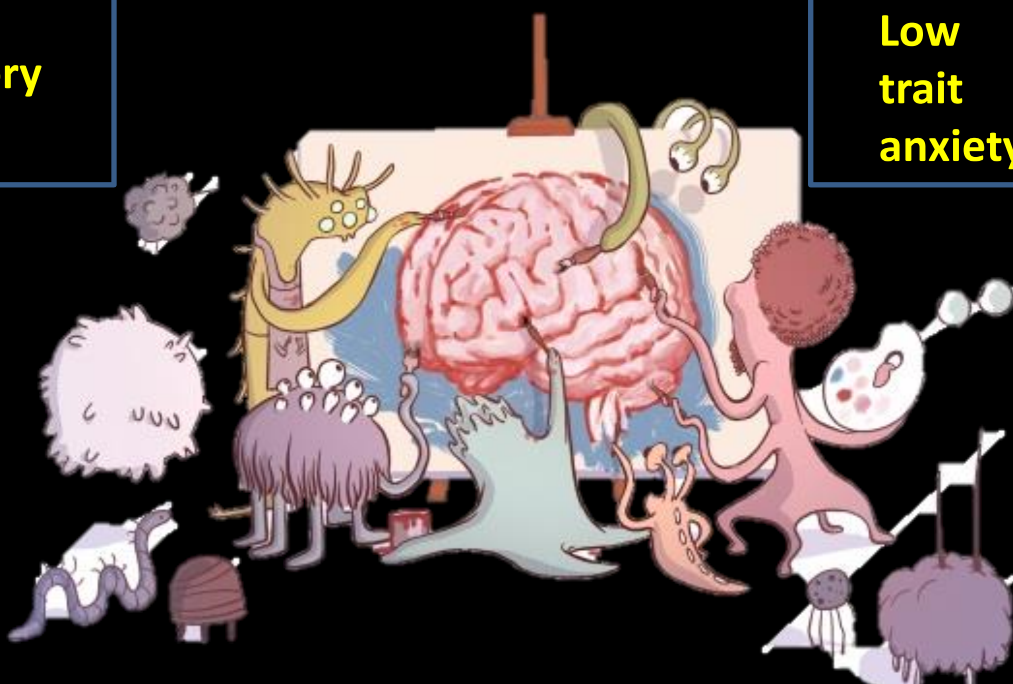
High inflammatory status

Low inflammatory status

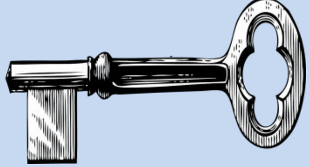



Increased anxiety-like behaviors

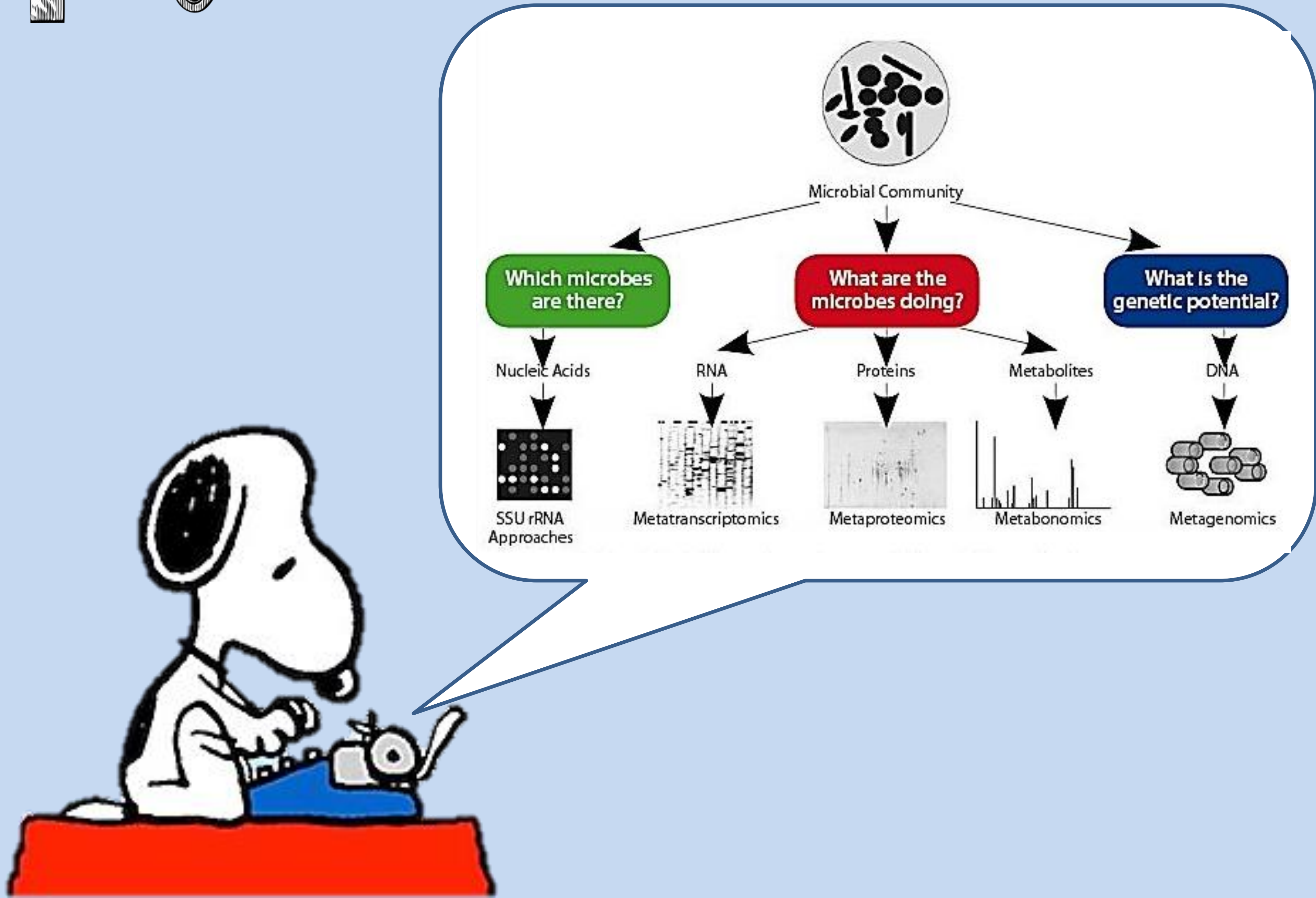
Low trait anxiety



J. A. Foster, K.A. McVey Neufeld. Cell, 2013

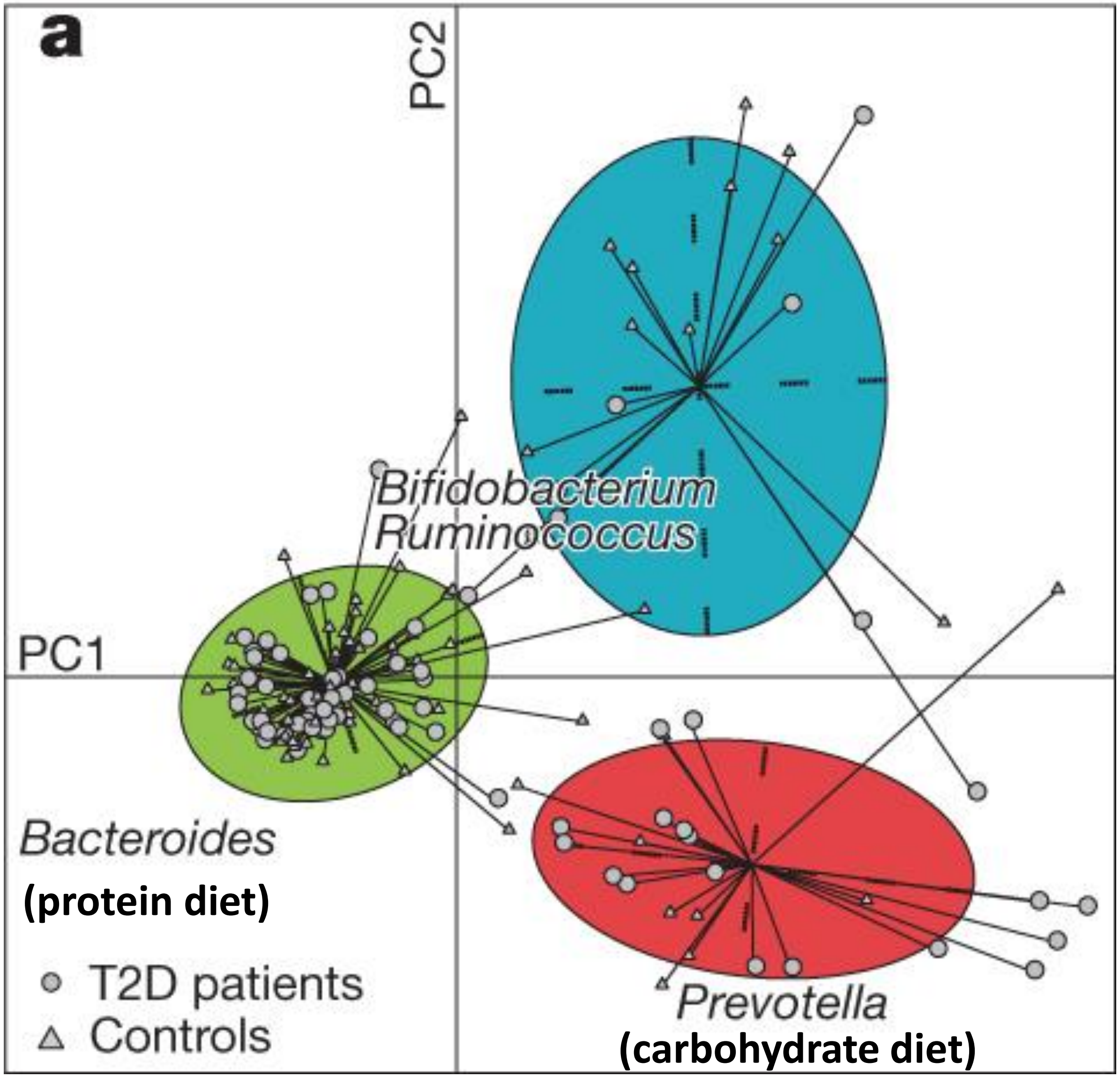


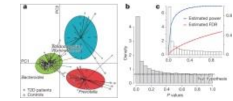
# Difficile studiarli.



# Gut Clusters

-Sciame,grappolo funzionalmente collegato-



Arumugam, 2011


Obesity
overweight
people
health
body
obese
leading
physical
energy
reduced
greater
increased
caused
mass
weight
problems
cases
due
may
BMI
reduce
effect
genes
likelihood
increasing
index
various
activity
limited
cause
authorities
pre-obese
metabolism
perceived
preventable
solely
extent
wealth
height
dietary
primary
calories
Western
type
medical
average
dieting
compares
support
worldwide
commonly
ability
drugs
expenditure
history
length
many
serious
still
maintain
view
satiation
cancer
stigmatized
Evidence
counterparts
century
appetite
difficulties
prevalence
increases
lack
sleep
measurement
genetic
children
required
types
diseases
gain
excess
times
world
taken
one
susceptibility
supplement
inhibit
osteoarthritis
breathing
particularly
parts
disease
adverse
little
earlier
endocrine
combination
though
case
medications
illness
excessive
diabetes
disorders
condition
modern
defines
fertility
placed
21st
treatment
volume
food
life
sovereign

↑ Firmicutes

↓ Bacteroidetes

↑ Proteobacteria

High fat diet

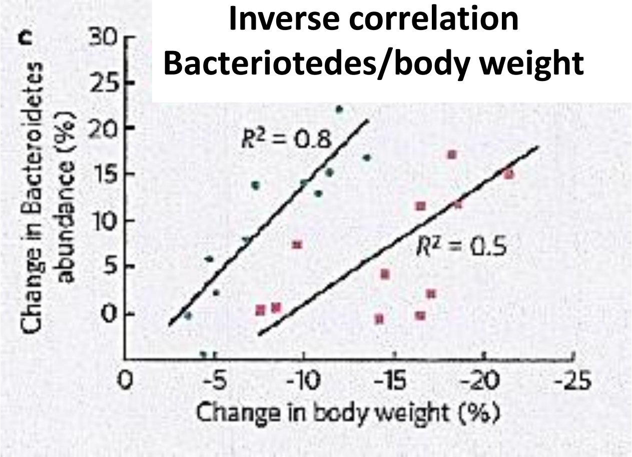
↓ Firmicutes

↑ Bacteroidetes

Food restriction

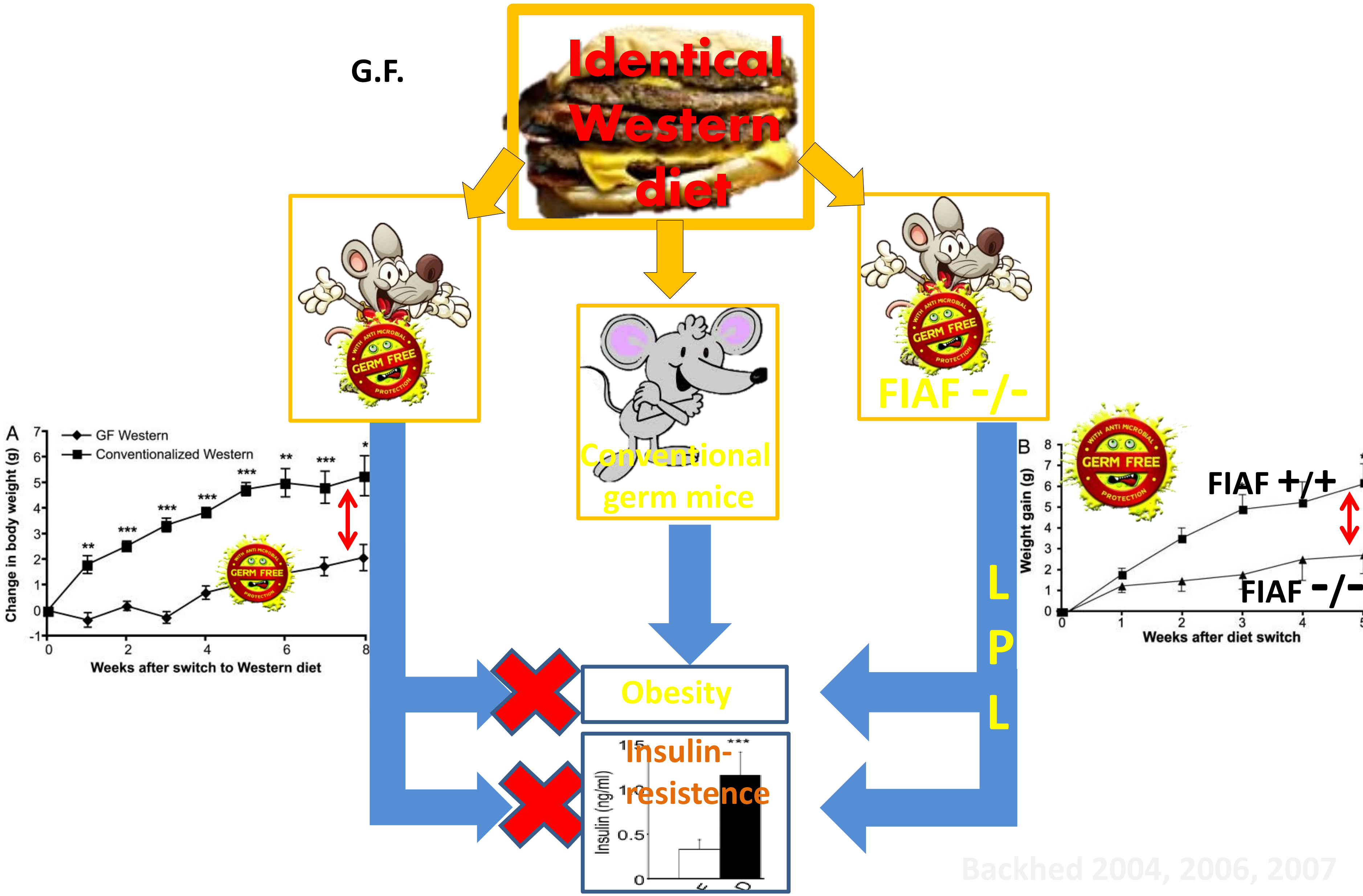
Low fat or low CHO

Inverse correlation
Bacteriotedes/body weight

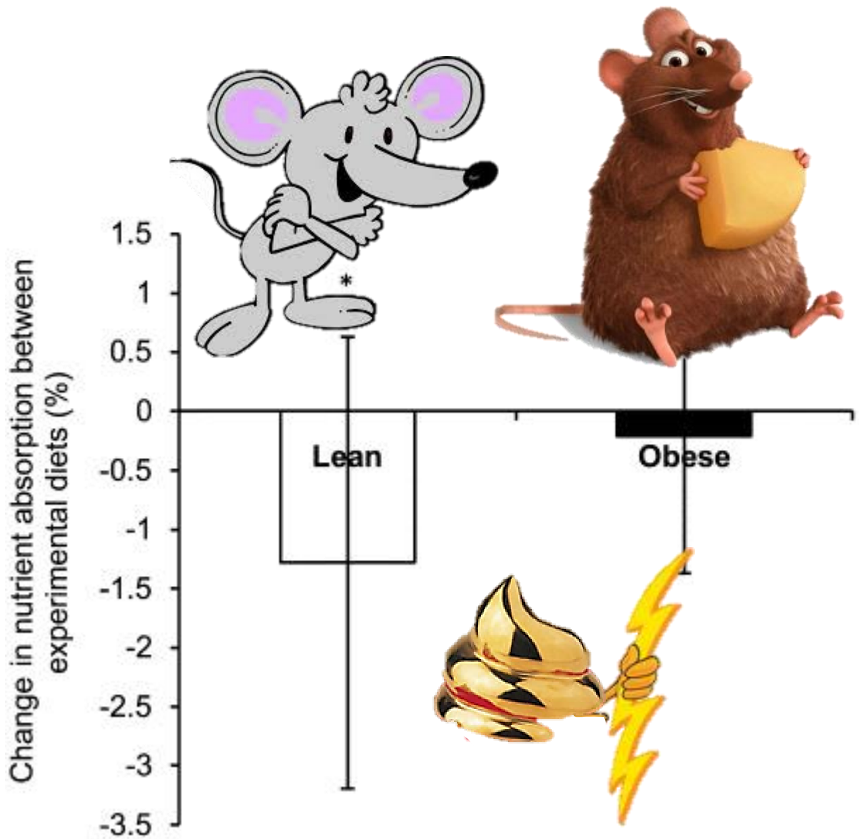



Gordon J, 2004
Ley ER et al. Nature 2006;

# The «obesity microbiota»

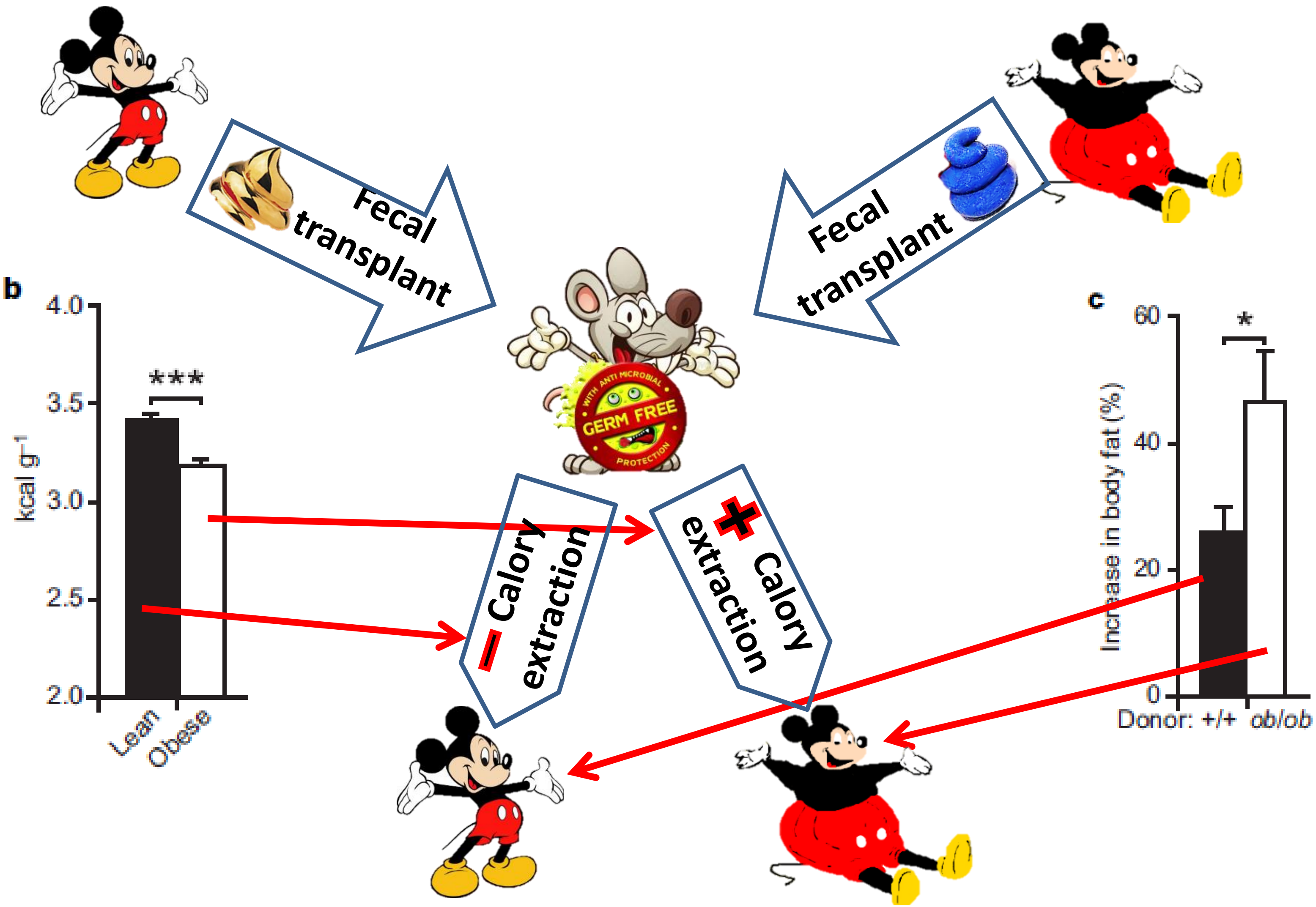


# The «obesity microbiota» extracts more nutrients from identical diet



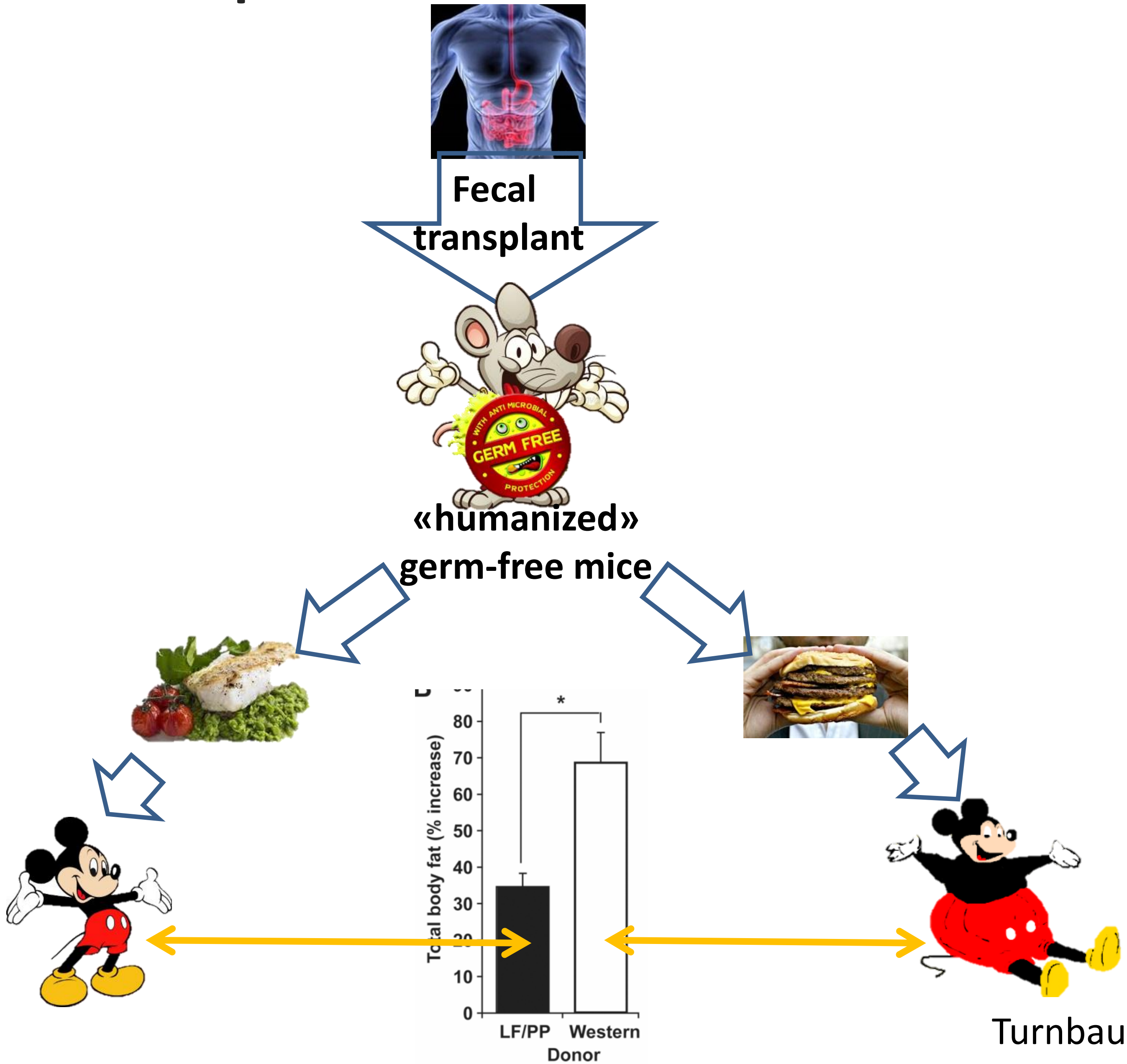

Jumpertz 2011

# The «obese microbiota» extracts more energy from the diet and is transplantable



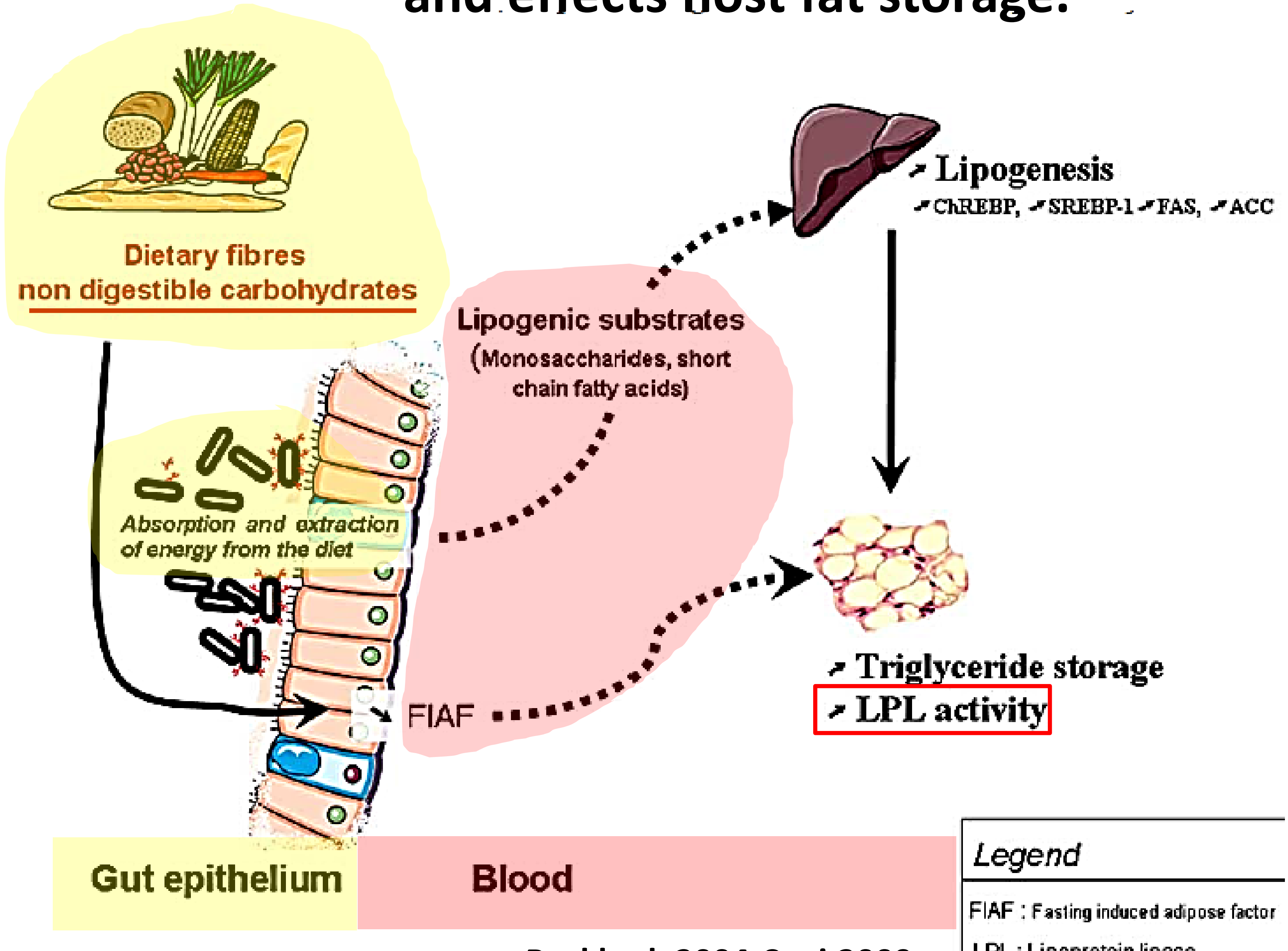

Turnbaugh,2006

# The «obese microbiota» is transplantable from man to mice




Turnbaugh 2009

# How the gut microbiota extracts more energy and effects host fat storage.




Backhed, 2004;Cani,2009

# Microbiota

Fermentazione
Carboidrati

↓

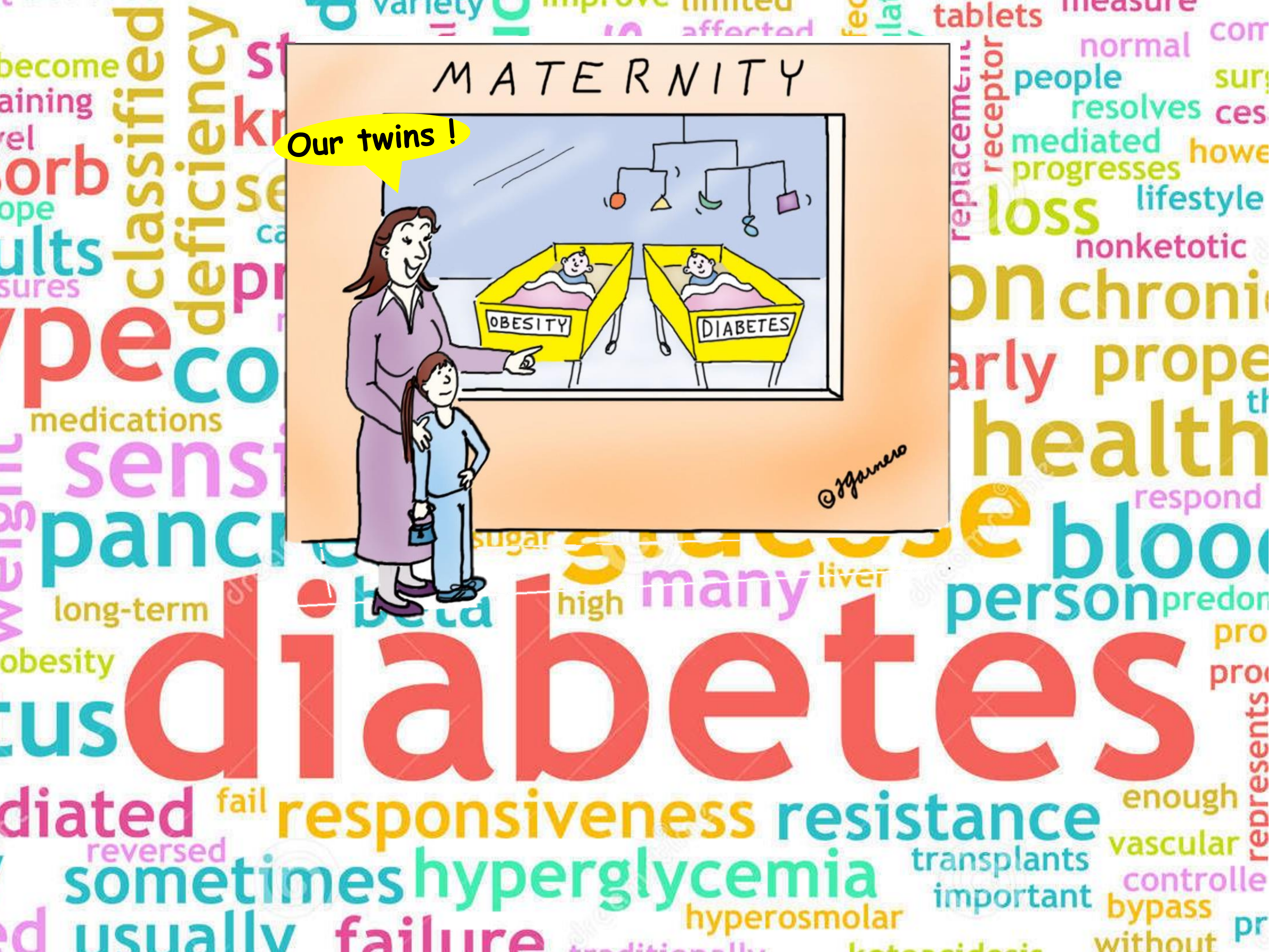
Monosaccaridi
SCFA

↓

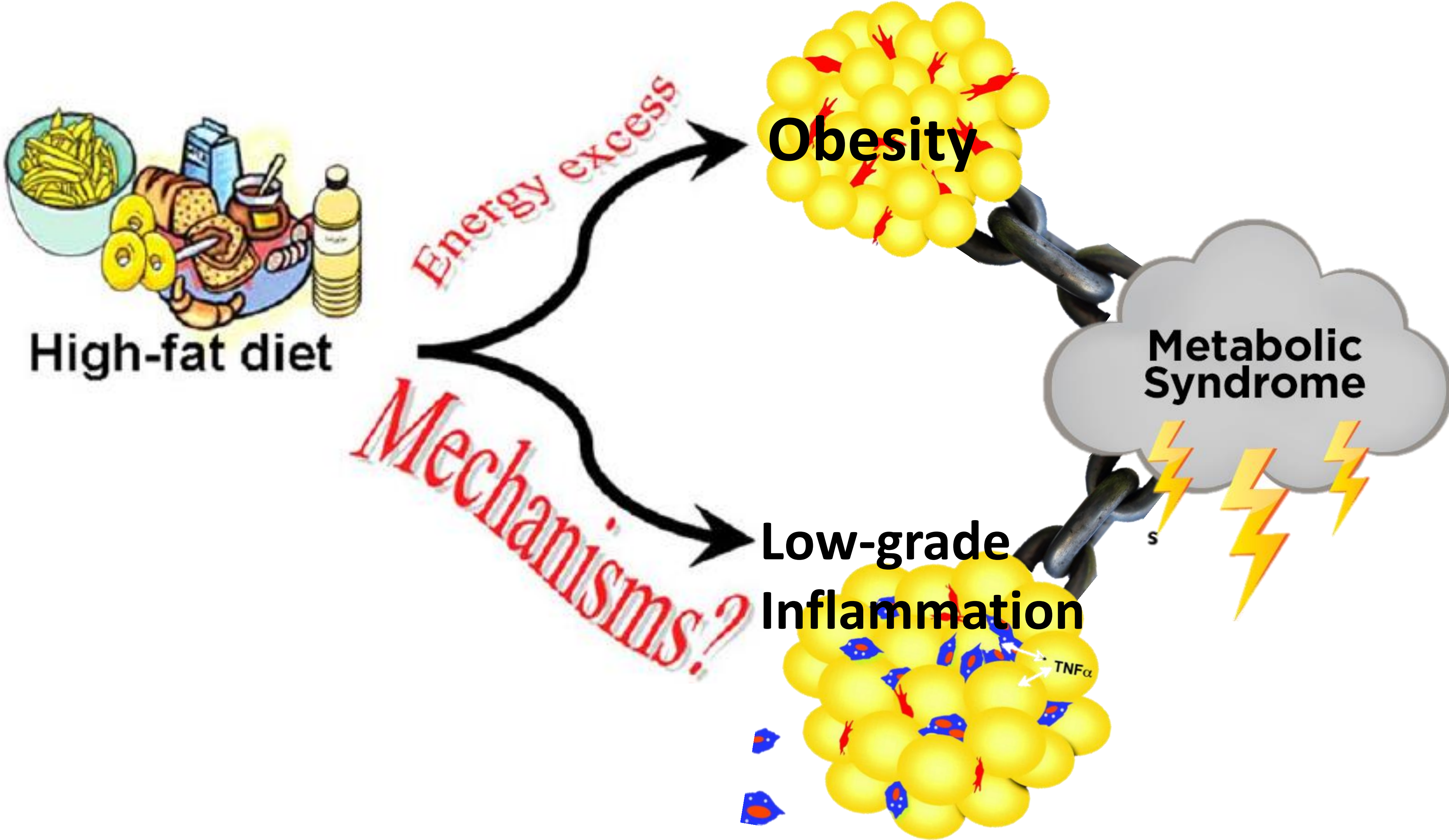
+ calory extraction
+ fat storage

# Obesità

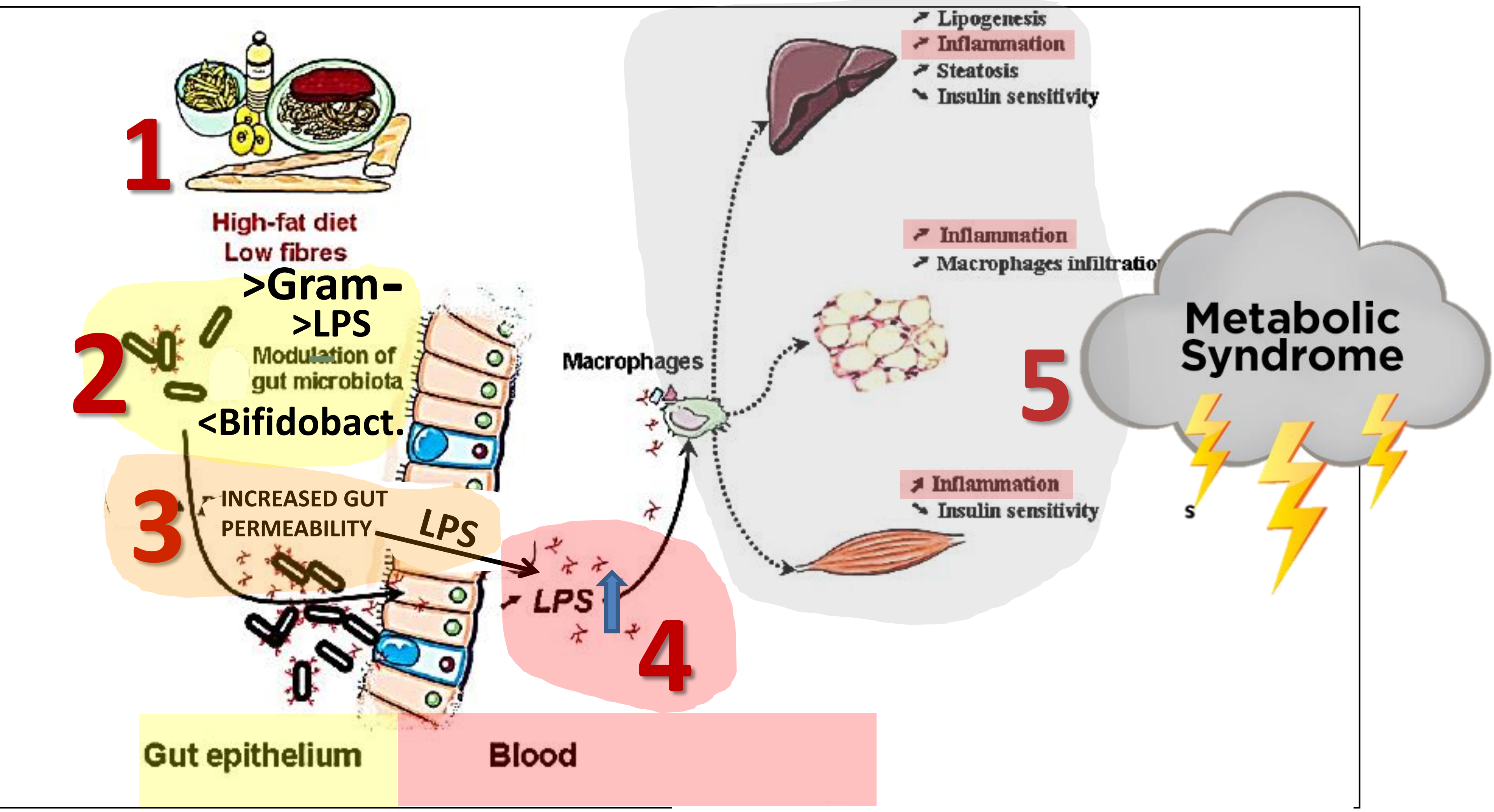

Microbiota:
Ruolo centrale
in obesità.


MATERNITY
Our twins !
OBESITY
DIABETES
©JGarnero

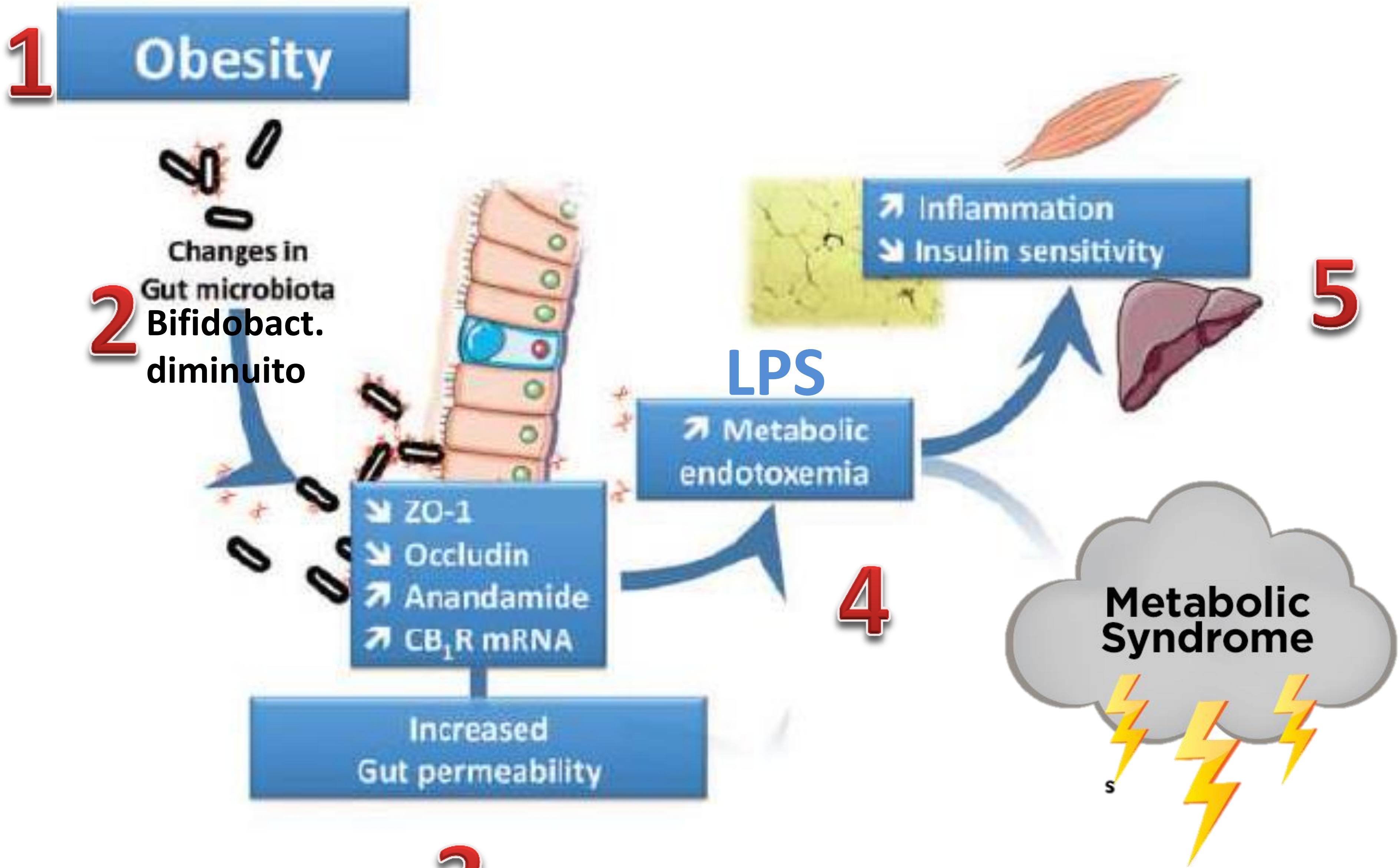
# Dall'obesità al diabete:
# Quale ruolo per il microbiota?



# Microbiota e Sindrome metabolica

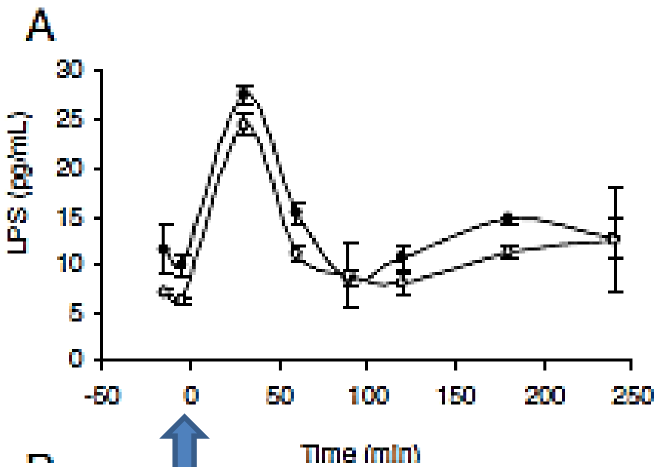


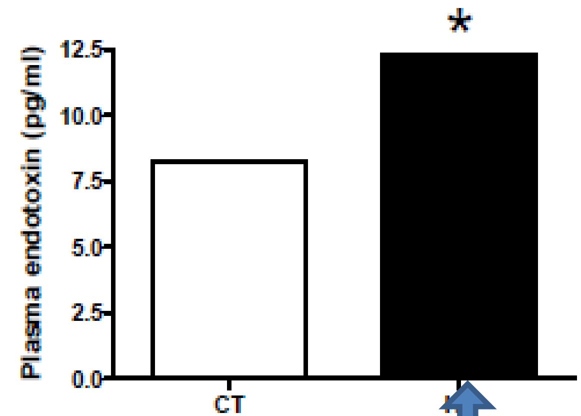

Tremaroli and Backhed Nature 09/ 2012




Cani et al Gut Microbes, 2012

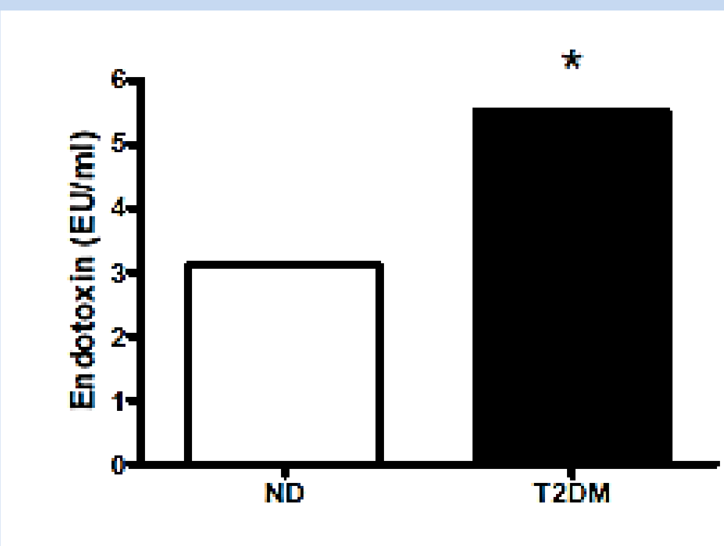
# LPS and H.F.diet in man



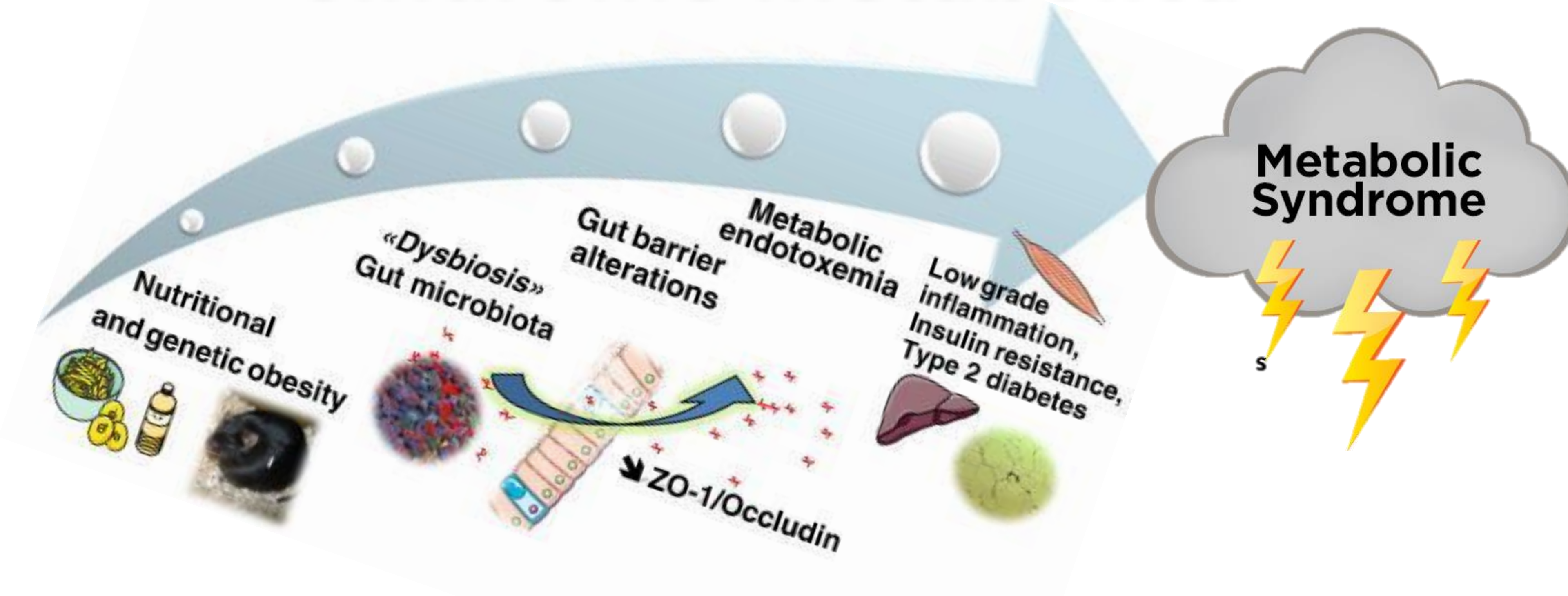

**Endotoxemia** correlates with fat intake in healthy men (*Erridge et al Am J Clin Nutr*

# LPS in T2 D.M. pts.

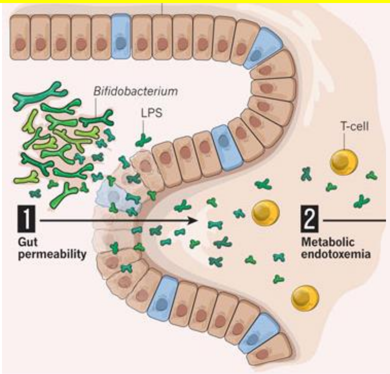



**Endotoxemia** positively correlates with fasting insulinemia, glycemia, total cholesterol, and/or triglycerides in type 2 diabetic patients ***(Creely et al Am J Physiol 2007; Al-Attas et al Cardiovascular Diabetology 2009).***

# Sindrome metabolica




**Microbiota ➡ Permeabilità intestinale ➡ endotoxemia**




## MICROBIAL INFLUENCE

Research by Patrice Cani, at the Université Catholique de Louvain in Brussels, has shown that, in mice, a decrease in the population of bifidobacteria species in the gut causes the tight junctions between the cells of the gut lining to loosen. The loose junctions increase the gut's permeability and allow lipopolysaccharide (LPS) from these microbes to leak through the gut wall. The resulting metabolic endotoxaemia causes a low-grade inflammation and can induce a number of metabolic disorders – including the insulin resistance that characterizes T2D.

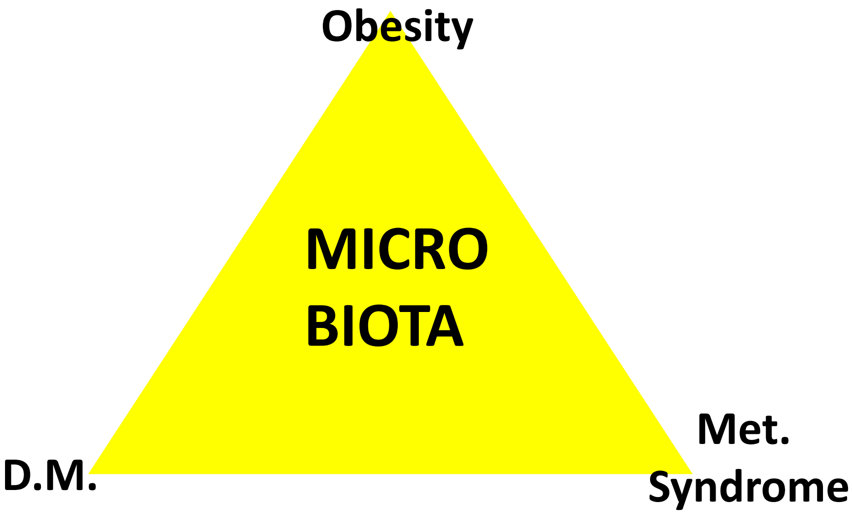
# Gut microbiota, obesity and related metabolic disorders
**(Linking arguments)**

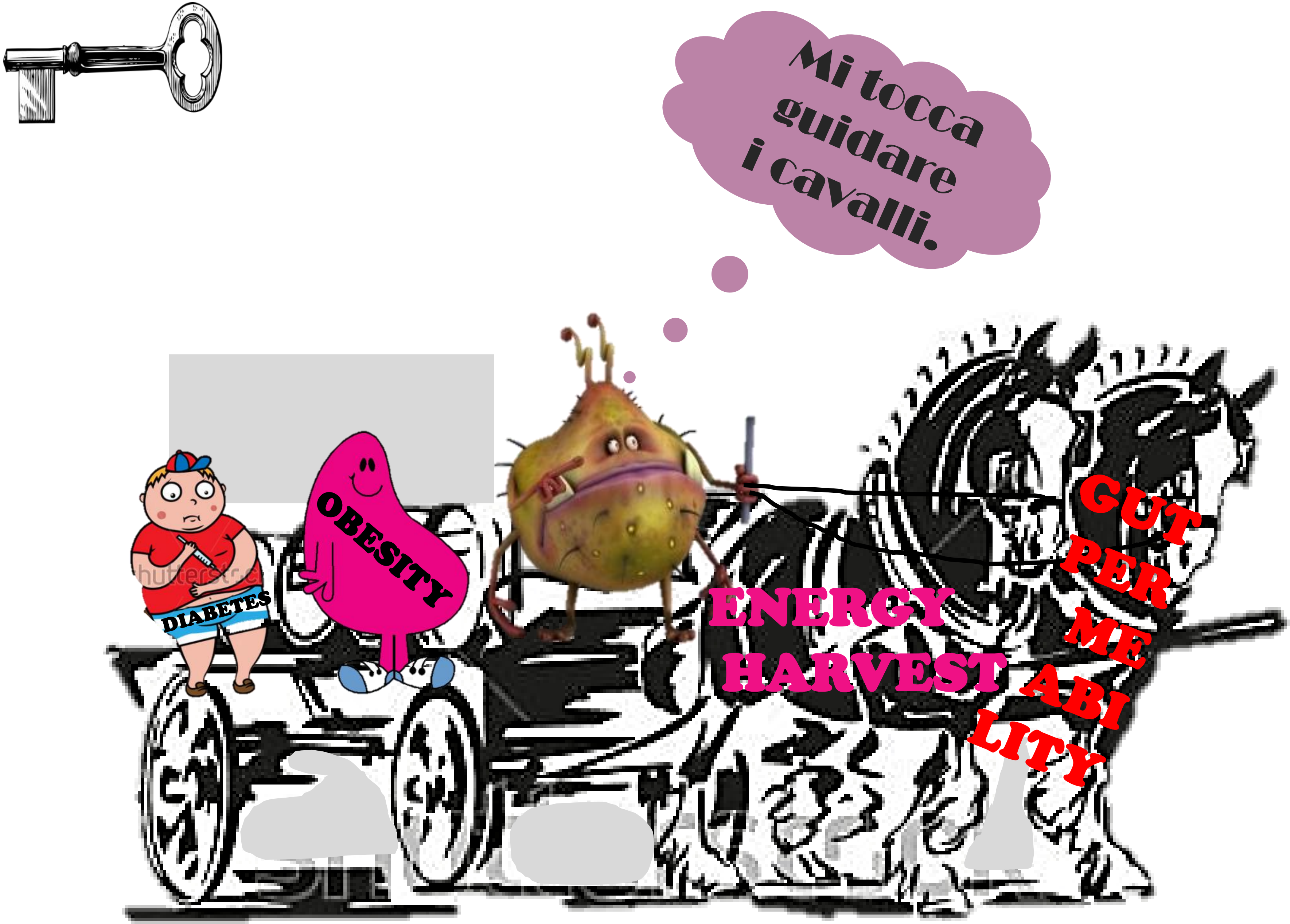
- Dysbiosis (changes in gut microbiota composition/function) occurs in diabetic and obese versus lean individuals

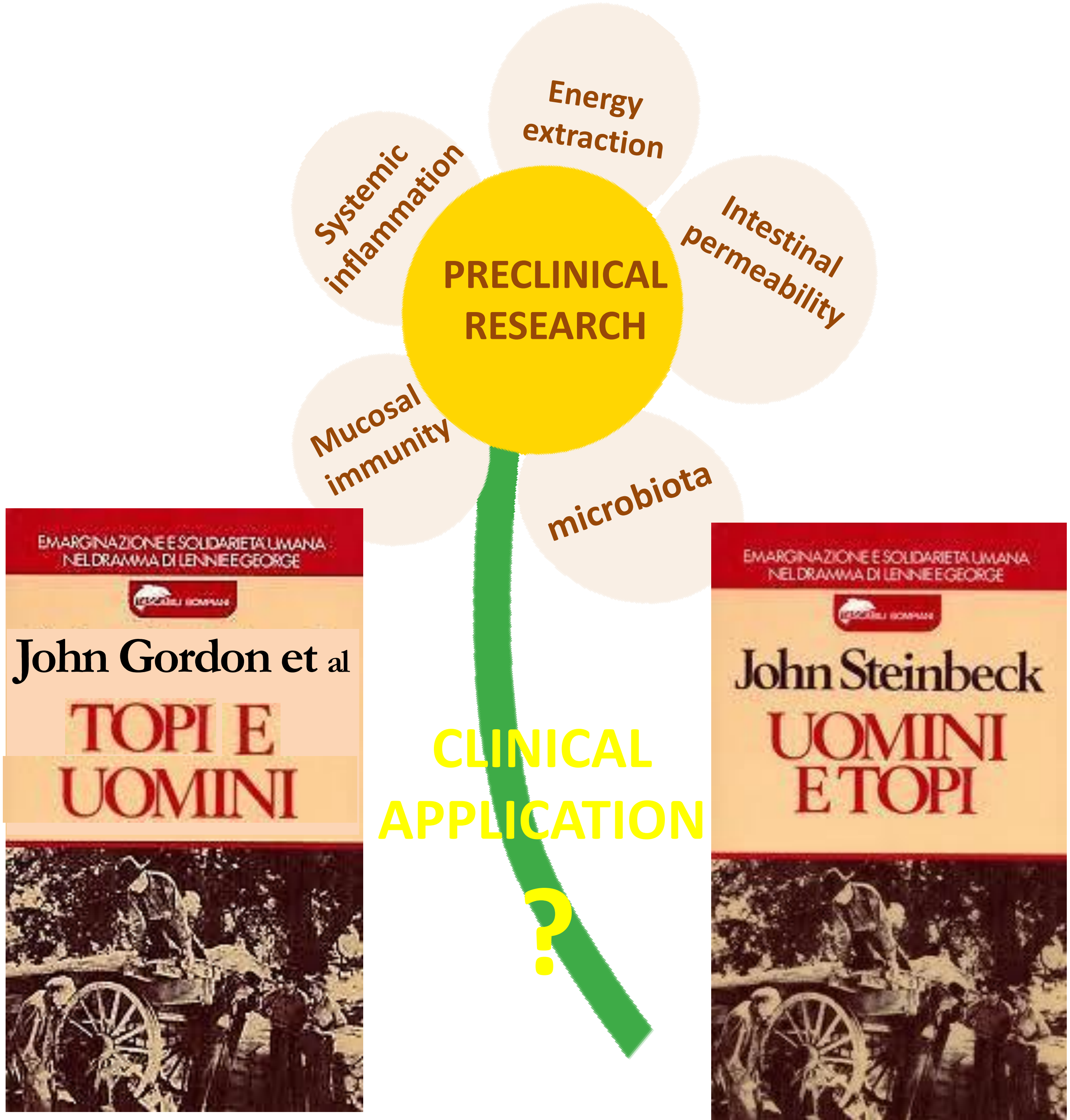
- Some components present in the gut microbiota play a harmful role in the context of obesity and diabetes (LPS)…

- The diet takes part in the modulation of the gut microbiome and microbiota composition/function in obesity and related metabolic disorders

*; reviews : Ley et al Gastroenterology 2010;Delzenne et Nature Rev endocrinol 2011; Cani et al Pharmacol Ther 2011; Tilg and Kaser JCI 2011,Tremaroli and Backhed Nature Sept 2012;



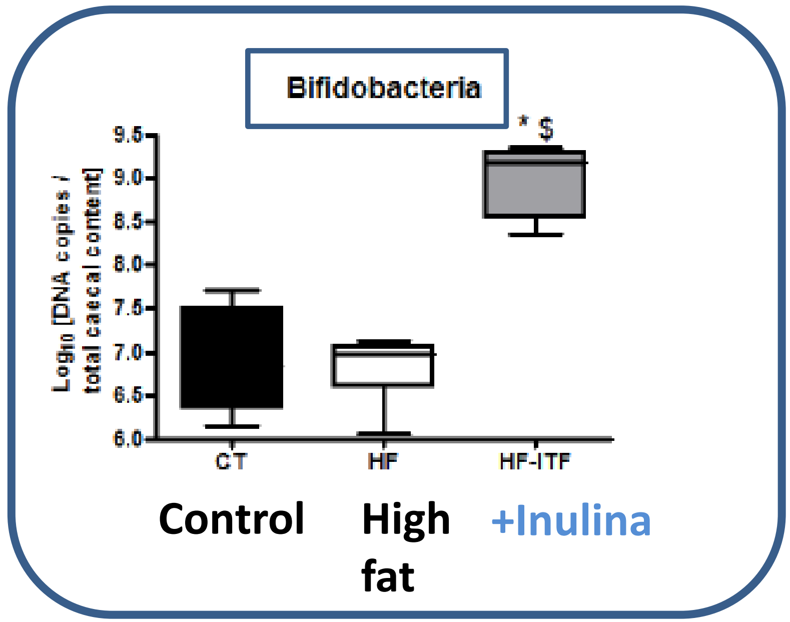

Mi tocca guidare i cavalli.
DIABETES
OBESITY
ENERGY HARVEST
GUT PER ME ABI LITY



EMARGINAZIONE E SOLIDARIETÀ UMANA
NEL DRAMMA DI LENNIE E GEORGE
John Gordon et al
TOPI E
UOMINI
Systemic inflammation
Energy extraction
Intestinal permeability
PRECLINICAL RESEARCH
Mucosal immunity
microbiota
CLINICAL APPLICATION
?
EMARGINAZIONE E SOLIDARIETÀ UMANA
NEL DRAMMA DI LENNIE E GEORGE
John Steinbeck
UOMINI
E TOPI

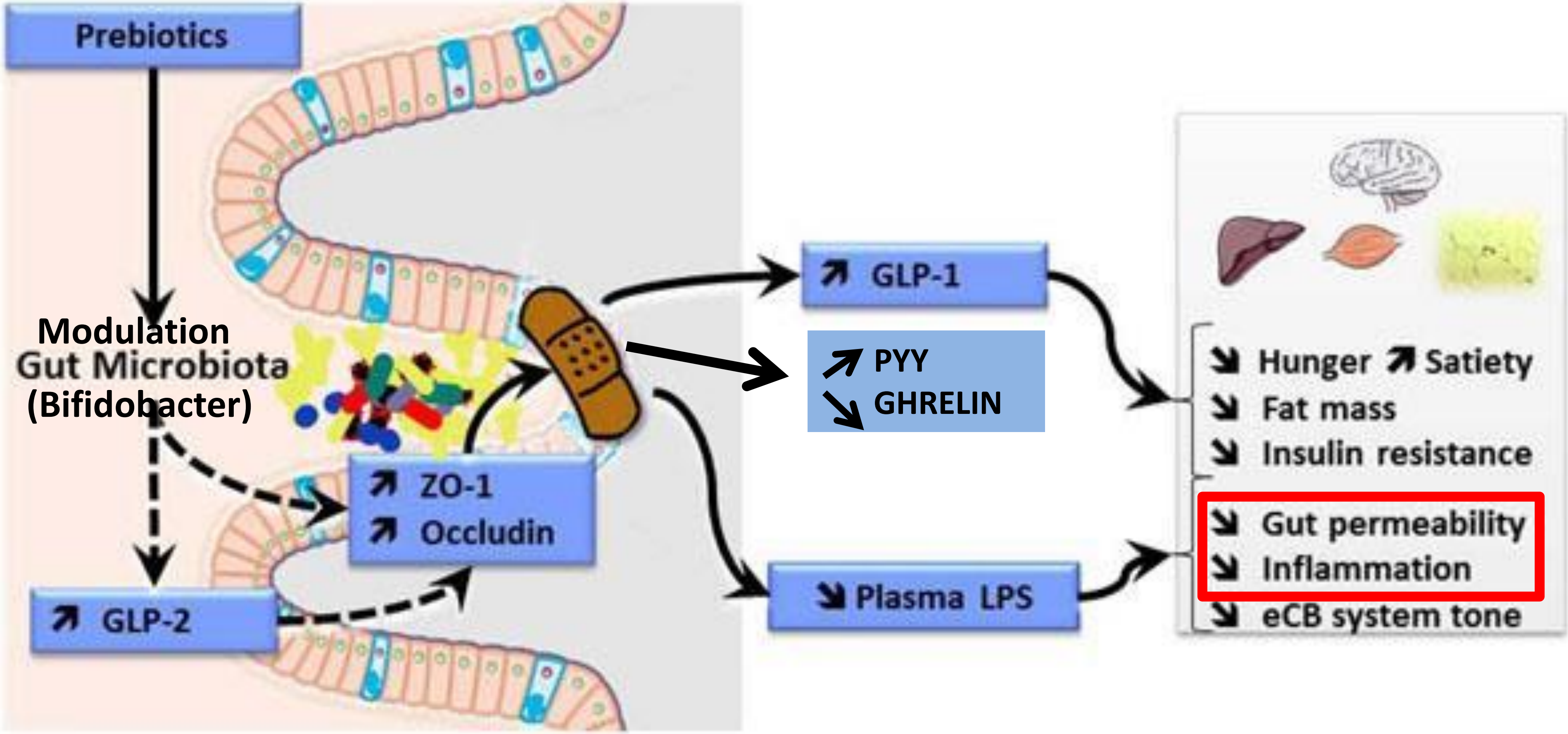
# PREBIOTICS and MICROBIOTA

Prebiotic approach : « non digestible » nutrients, that escape the digestion in the upper part of the gut , but can be fermented by bacteria, thereby leading to the selective promotion of bacteria (or bacterial functions) that may be helpful for the control of metabolic disorders associated with obesity *Gibson and Roberfroid. J. Nutr. 125. 1401. 1995; Roberfroid et al Br J Nutr 2010;*


*Cani et al Diabetologia, (2007), Gut (2009); Neyrinck et al J Nutr Biochem, ( 2011); Neyrinck et al PlosOne (2011)*

# PREBIOTICS and MICROBIOTA

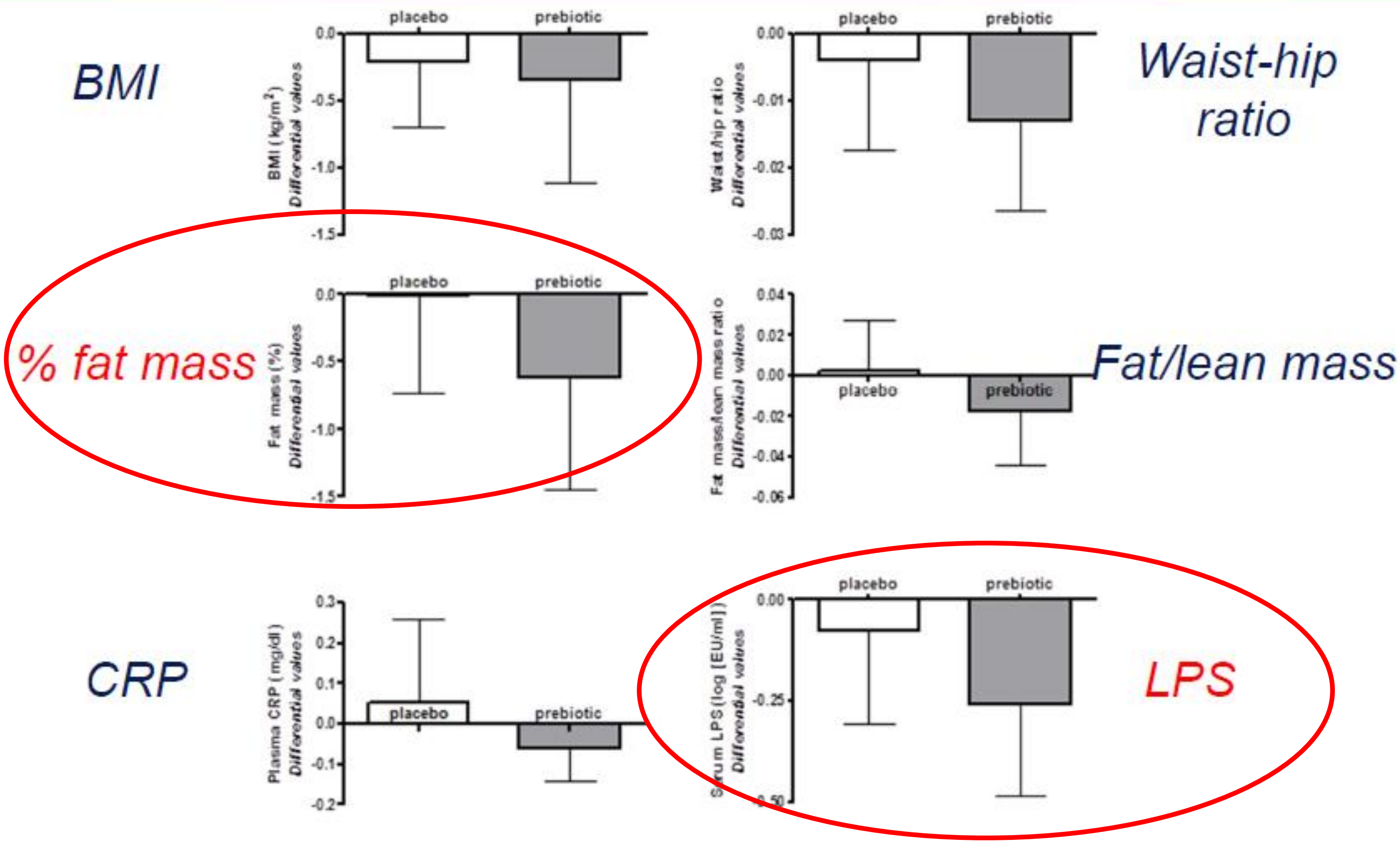



Delzenne, 2011

# Exploratory intervention study with inulin-type fructans in obese women : focus on gut microbiota *(Dewulf et al, Gut 2012)*

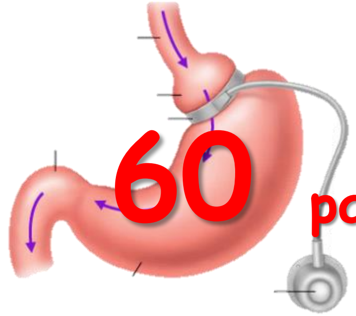
**(n=15; doppio ceco)**

## Changes in anthropometric and serum parameters



N. Basso, A. Redler, P. Marini, G. Mingrone, MG. Carbonelli, L. Papa, G. Casella, E. Soricelli

# Prebiotics and Surgery



**60** patients

Randomizzazione

| 30 Pts | 30 Pts |
|---|---|
| **CONTROL**<br>PLACEBO (MALTODESTRINE) | **INULINA**<br>(PREBIOTICO) |

## Follow up: 1, 3, 6 months

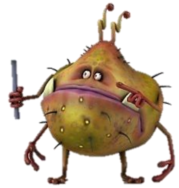
EWL, SCFAs, Lipopolisaccaridi, PCR, H2 Breath Test, insulinoresistenza

# MICROBIOTA e CHIRURGIA

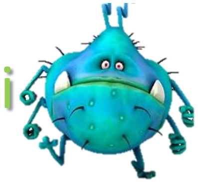
# Changes by

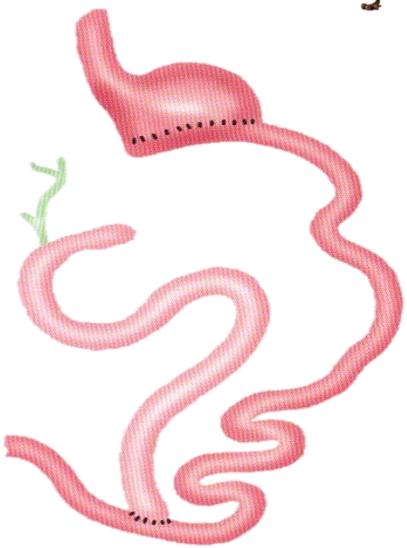
| Bariatric Surgery | | Gut Microbiota |
|---|---|---|
| ✓ | WEIGHT LOSS | ✓ |
| ✓ | T2DM IMPROVEMENT | ✓ |
| ✓ | ↑ GLP-1, GIP, PYY | ✓ |
| ✓ | ↓ GHRELIN, LEPTIN | ✓ |
| ✓ | ↑ ENERGY EXPENDITURE | ✓ |
| ✓ | ↓ INFLAMMATION | ✓ |

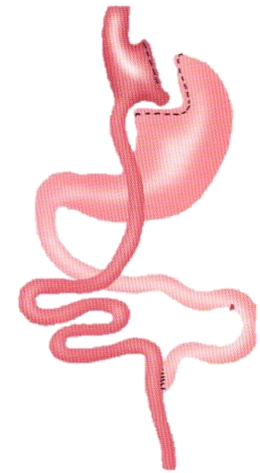
# Microbiota umano dopo chirurgia bariatrica



## Fattori di variazioni







Effetto dieta

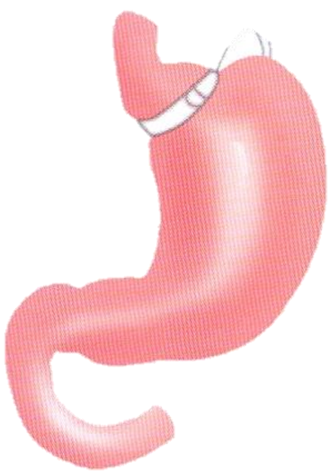
-By pass gastrointestinale
-Diversione entero-epatica
-Intestino «corto»
-Accelerato transito

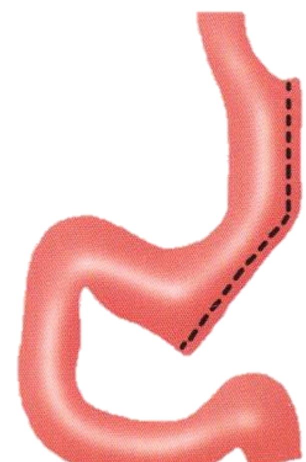
-HCl in piccolo intestino
+ $O_2$ disciolto in intestino
⬇
-Favoriti anaerobi facoltativi vs obbligatori

+ Acidi biliari

-Rilocazione di microbiota da tenue a colon

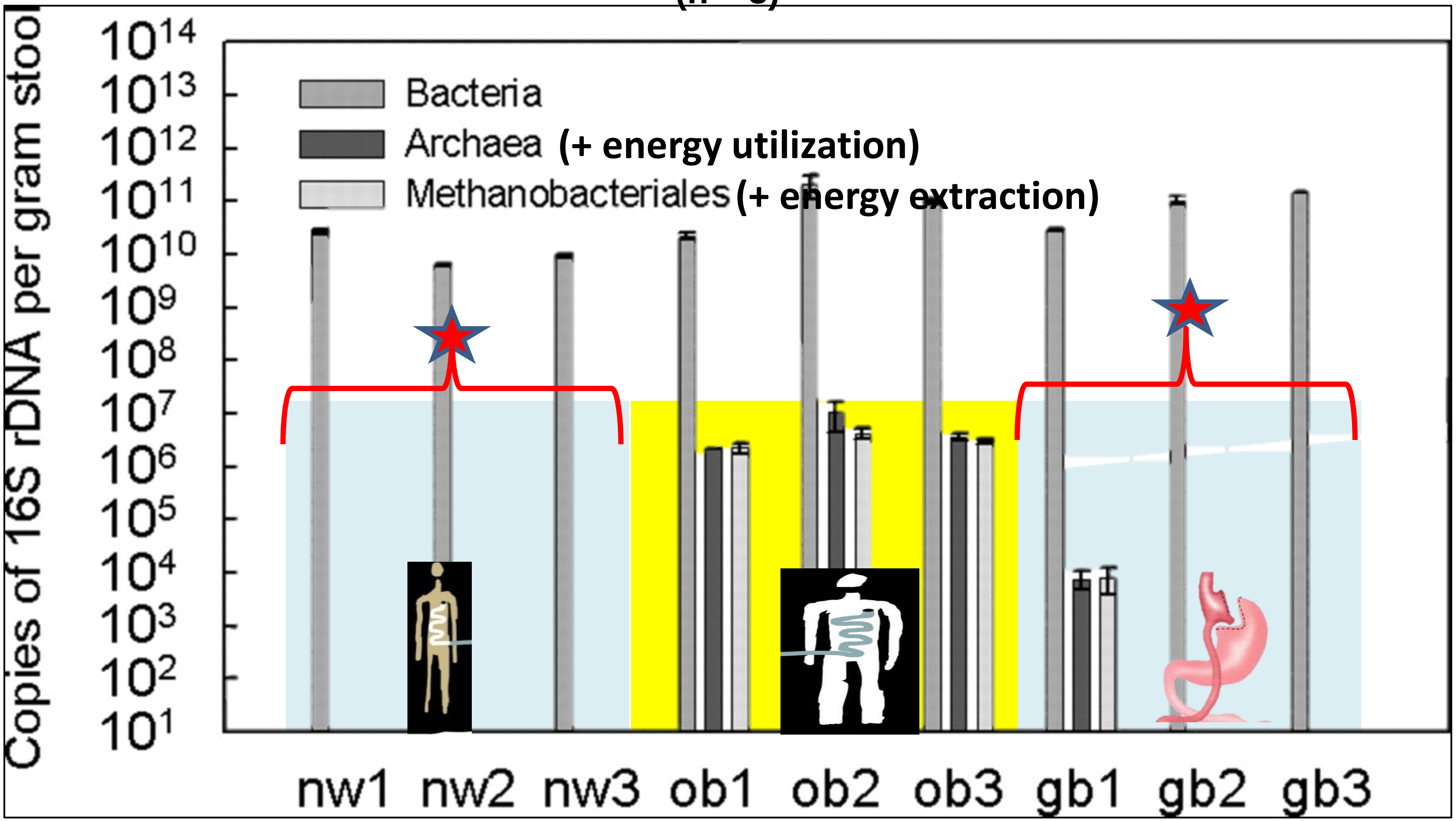
-Effetto B.R.A.V.E.





# Microbiota and RyGBP

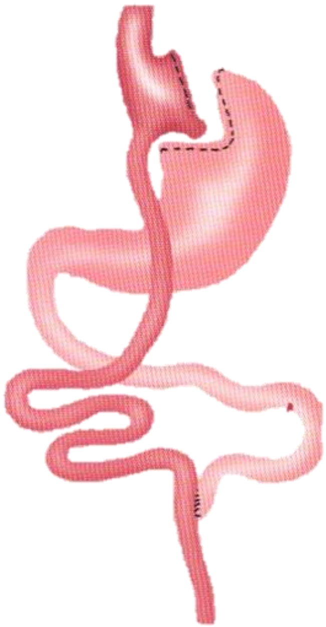
**The numbers of Bacteria, Archaea, and Methanobacteriales quantified by real-time QPCR. (n = 3)**




Zhang H et al. PNAS 2009;106:2365-2370

PNAS

# Microbiota and RyGBP



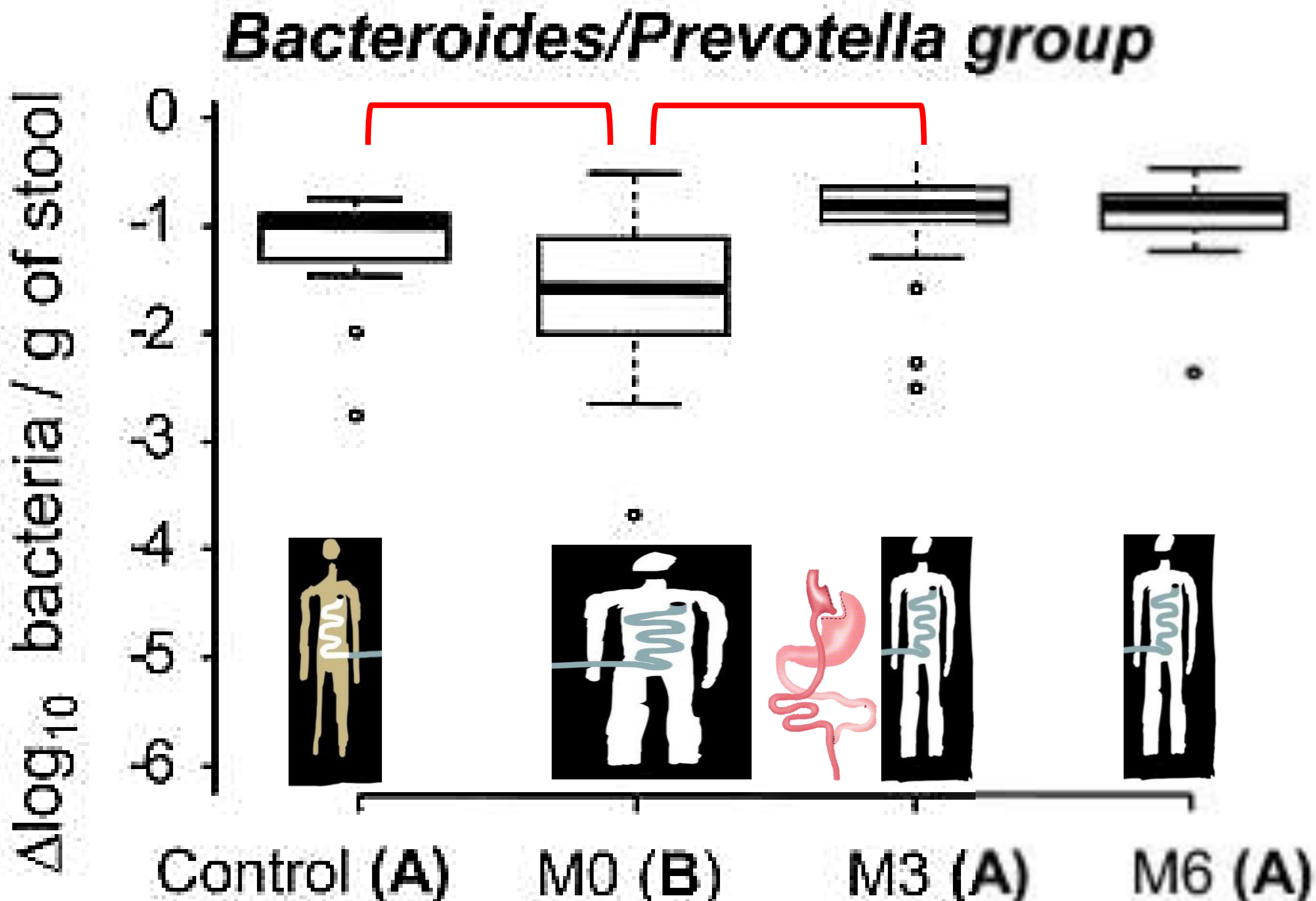
Bacteroidetes — producing
Archeae — utilizing
$H_2$

+SCFA
+ENERGY
OBESITY

## Differential Adaptation of Human Gut Microbiota to Bariatric Surgery–Induced Weight Loss

Links With Metabolic and Low-Grade Inflammation Markers

**Furet ,2010**

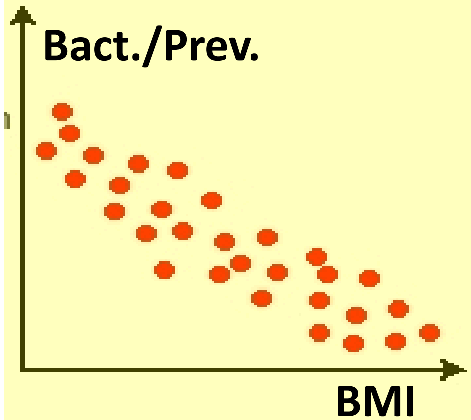



(Normopeso)

Obeso Pre op

Obeso post op

Obeso post op



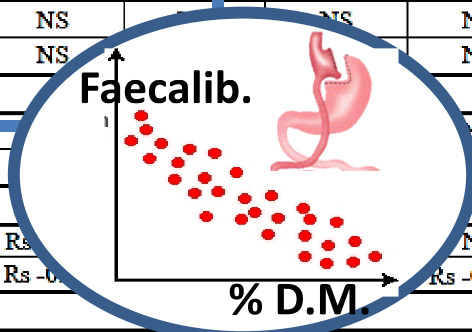

The higher the increase in the proportions of Bacteroides/ Prevotella,
the better the reduction in body fat mass and plasma leptin

# Microbiota and RyGBP

B

| | Body weight | BMI | Body fat mass | Leptin | Calorie intake | Fasting glucose | Insulin | Adipo-nectin | hsCRP | Il-6 | Orosomucoid |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Bacteroides /Prevotella* | | | | | | | | | | | |
| OB/nD + OB/D | Rs -0.33† | Rs -0.35† | Rs -0.32† | Rs -0.43† | Rs -0.3[illegible]* | Rs -0.28* | NS | NS | Rs -0.27* | NS | Rs -0.31* |
| OB/nD | Rs -0.3* | Rs -0.3* | NS | Rs -0.39† | Rs -0.3[illegible]* | Rs -0.36* | NS | NS | Rs -0.32* | NS | |
| *C.leptum* | | | | | | | | | | | |
| OB/nD + OB/D | NS | NS | NS | NS | [illegible] | NS | NS | NS | Rs -0.31* | NS | NS |
| OB/nD | NS | NS | NS | NS | [illegible] | [illegible] | NS | NS | Rs -0.29* | NS | NS |
| *Faecalibacterium prausnitzii* | | | | | | | | | | | |
| OB/nD + OB/D | NS | [illegible] | NS | [illegible] | [illegible] | [illegible] | NS | NS | Rs -0.39† | Rs -0.35† | Rs -0.32* |
| OB/nD | NS | NS | NS | [illegible] | [illegible] | [illegible] | [illegible] | NS | Rs -0.37† | Rs -0.34† | Rs -0.30* |
| *E. coli* | | | | | | | | | | | |
| OB/nD + OB/D | Rs -0.42‡ | Rs -0.47§ | Rs -0.41‡ | Rs [illegible] | [illegible] | [illegible] | NS | NS | NS | NS | Rs -0.38† |
| OB/nD | Rs -0.41† | Rs -0.47‡ | Rs -0.45‡ | Rs -0.[illegible] | [illegible] | [illegible] | Rs -0.22* | Rs -0.33* | NS | NS | Rs -0.37* |
| *Bifidobacterium* | | | | | | | | | | | |
| OB/nD + OB/D | Rs 0.19† | Rs 0.17† | NS | Rs 0.34† | Rs 0.28* | NS | Rs 0.30* | NS | Rs 0.29* | NS | Rs 0.36† |
| OB/nD | NS | NS | NS | NS | NS | NS | Rs 0.29* | NS | NS | NS | Rs 0.36* |
| *Lactobacillus/Leuconostoc/Pediococcus* | | | | | | | | | | | |
| OB/nD + OB/D | NS | NS | NS | NS | Rs 0.29* | Rs 0.24* | Rs 0.28* | NS | NS | NS | NS |
| OB/nD | NS | NS | NS | NS | Rs 0.30† | NS | Rs 0.30* | NS | NS | NS | NS |

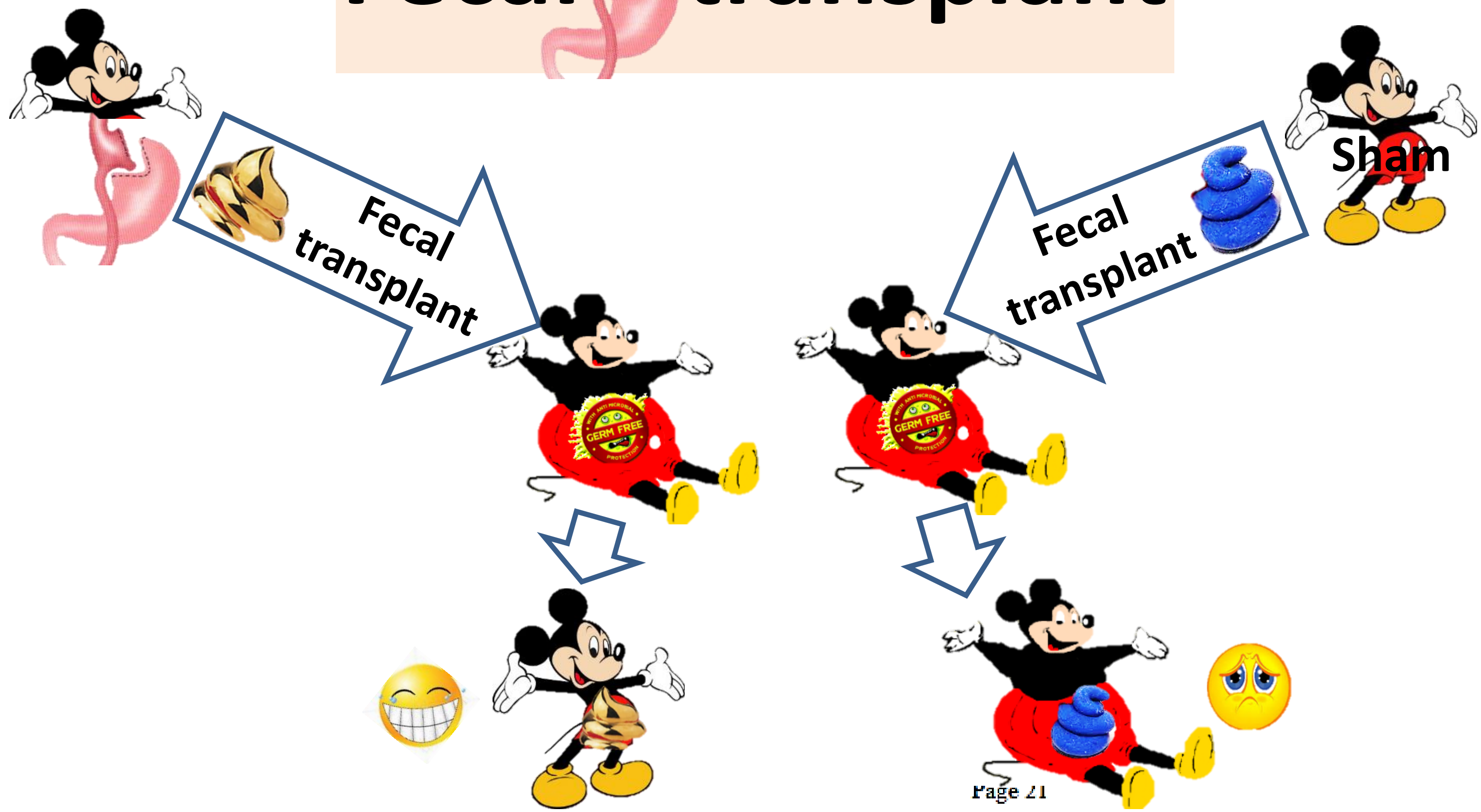
* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$, § $p < 0.0001$, ¶ $p < 0.00001$

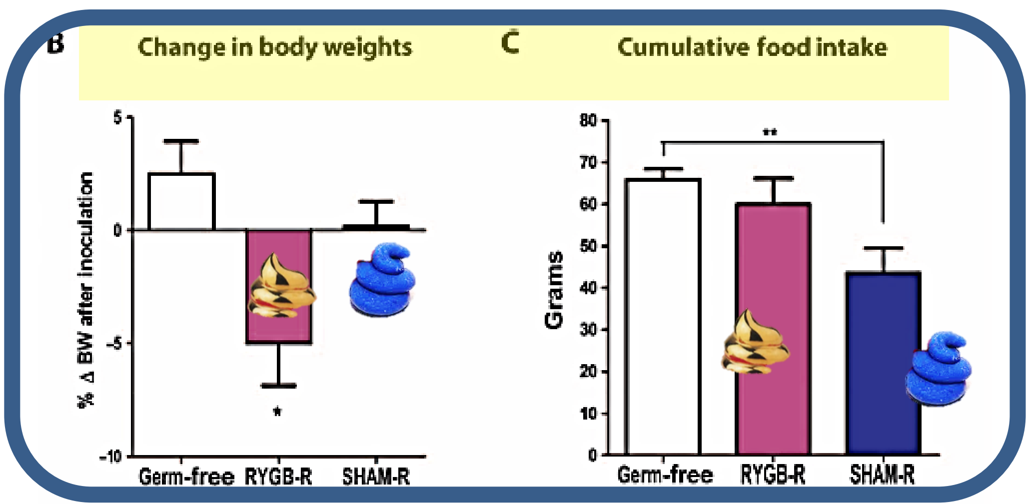



*Faecalibacterium prausnitzii* species inversely correlates with diabetes and is directly linked to the reduction in low-grade inflammation in human obese subjects submitted to Roux-en-Y Gastric bypass

(Furet *et al* Diabetes 59:3049–3057, 2010)

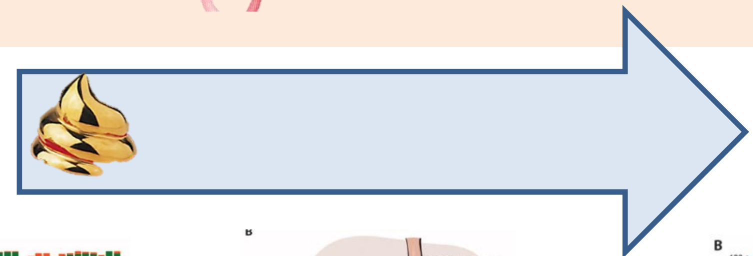
# Fecal transplant

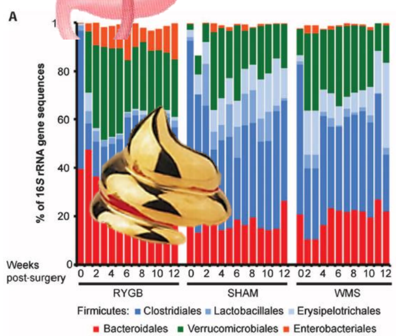


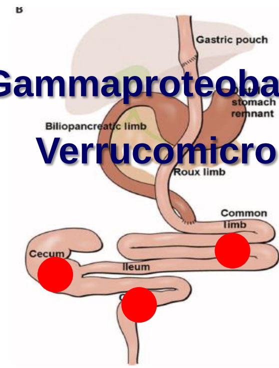



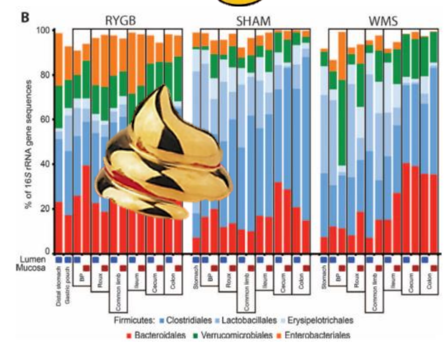

Liou, 2013

# Fecal transplant






| | RYGB-R | SHAM-R | GF |
|---|---|---|---|
| | 15 | 10 | 7 |
| od glucose (mg/dl) | 148 ± 5.5A | 147 ± 7.4A | 120 ± 3.9B |
| ulin (ng/ml) | 0.46 ± 0.10A | 0.99 ± 0.19A | 0.73 ± 0.19A |
| OMA-IR | 4.4 ± 0.98A | 9.8 ± 4.1A | 5.5 ± 1.5A |
| um triglyceride (mg/dl) | 77.8 ± 9.7A | 113 ± 8.5B | 73.5 ± 16.8A |
| um NEFA (meQ/liter) | 0.58 ± 0.06A | 0.65 ± 0.06A | 0.62 ± 0.05A |
| er weight (% body weight) | 4.9 ± 0.10A | 4.8 ± 0.20A | 4.8 ± 0.18A |
| er triglyceride (mg/g liver) | 22.9 ± 4.2A | 36.2 ± 9.1A | 21.6 ± 6.0A |

## RECEPIENTS

| RYGB-R | | SHAM-R |
|---|---|---|
| 15 | n | 10 |
| 148 ± 5.5A | Blood glucose (mg/dl) | 147 ± 7.4A |
| 0.46 ± 0.10A | Insulin (ng/ml) | 0.99 ± 0.19A |
| 4.4 ± 0.98A | HOMA-IR | 9.8 ± 4.1A |

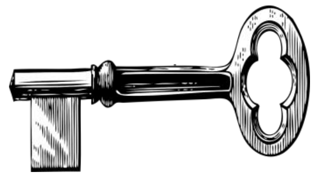
# Trapianto degli effetti di Ry-GBP

Liou, 2013

# WEIGHT LOSS

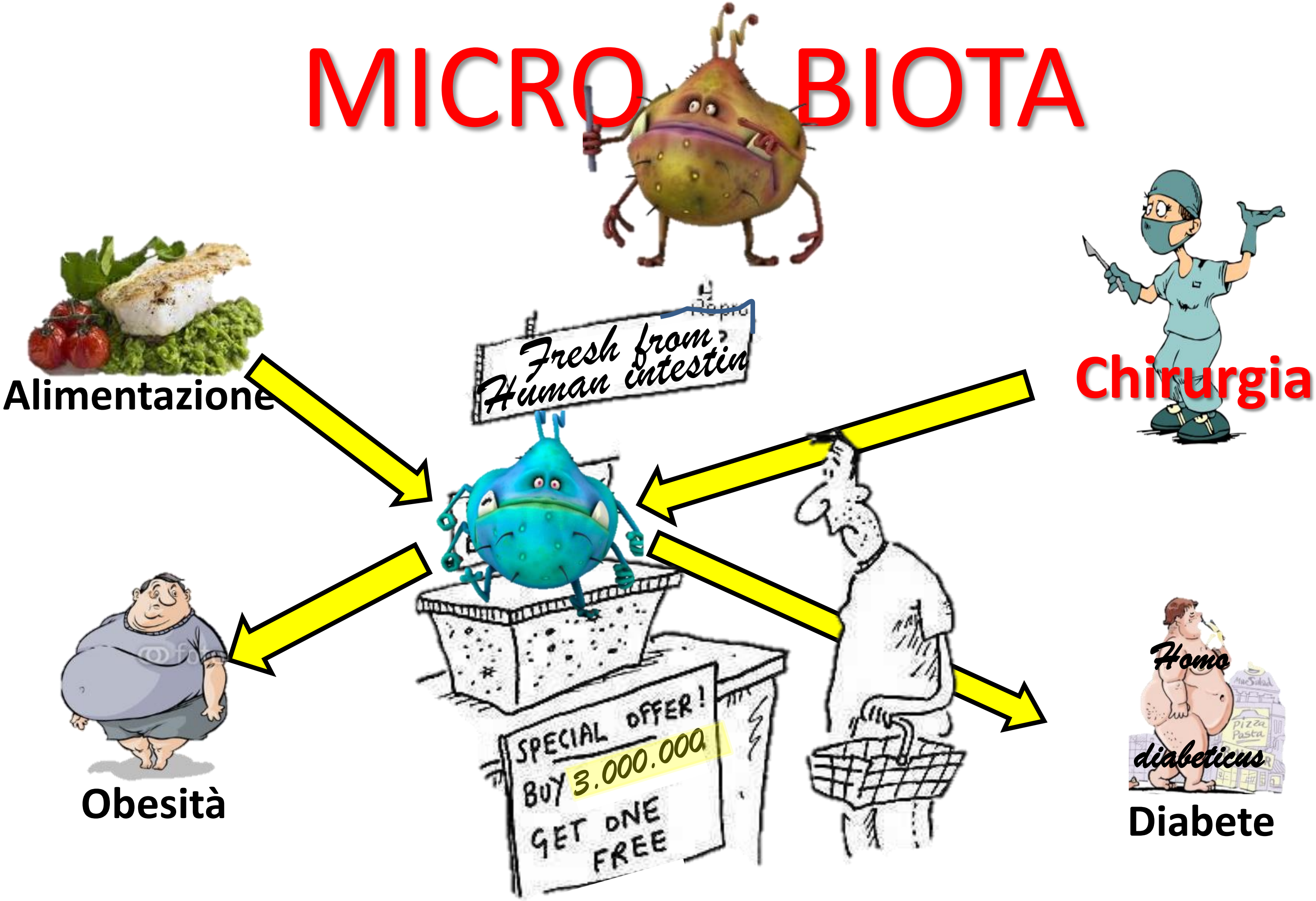
M
IL PESO


Pure io.



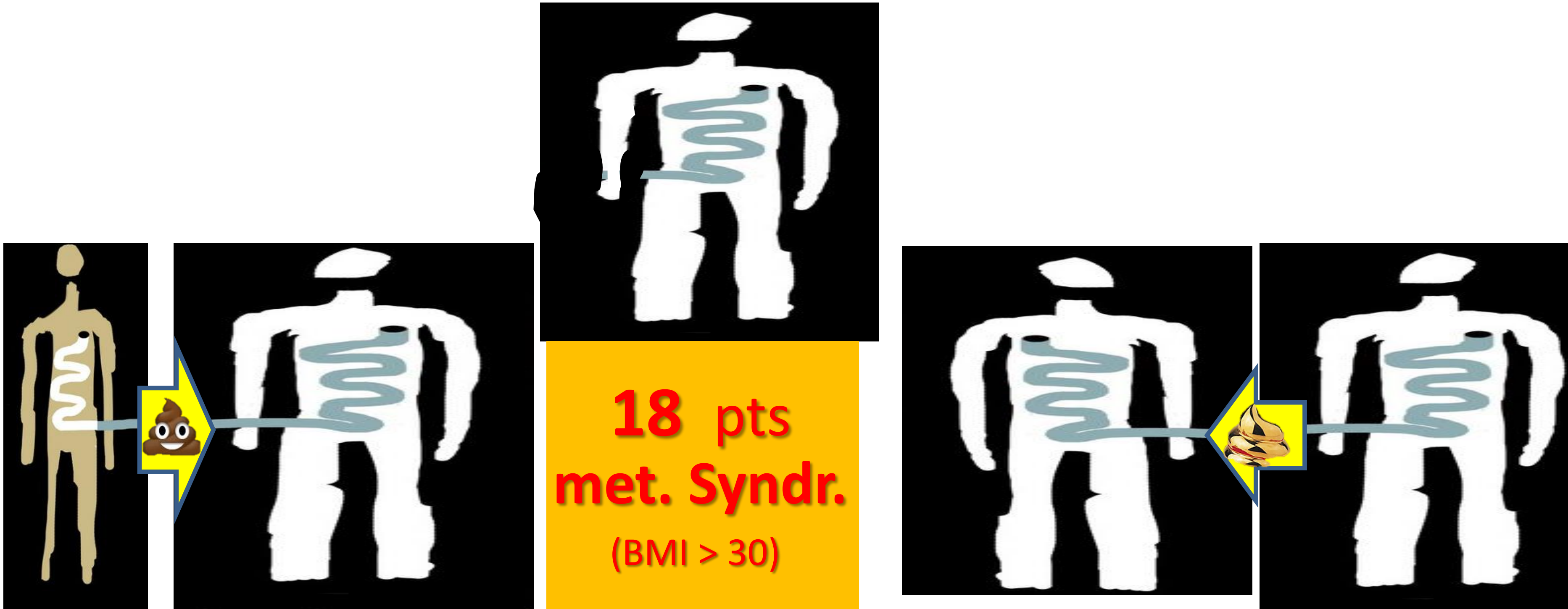
**Microbiota:**
**Modulati da chirurgia,**
**innescano i risultati.**

# MICRO BIOTA




# Come possiamo usarli ?

# Fecal transplant in man




| Lean donor feces | | Autologous donor feces |
|---|---|---|
| **9 pts** | | **9 pts** |
| **Lean donor** feces | ↓ **Insulin resistance** = (Euglycemic clamp) | **Autologous donor** feces |
| | ↓ **Fasting lipid levels** = | |

Vrieze A: 2013

# Fecal bacteriotherapy: other clinical scenarios?

JOHNS HOPKINS MEDICINE

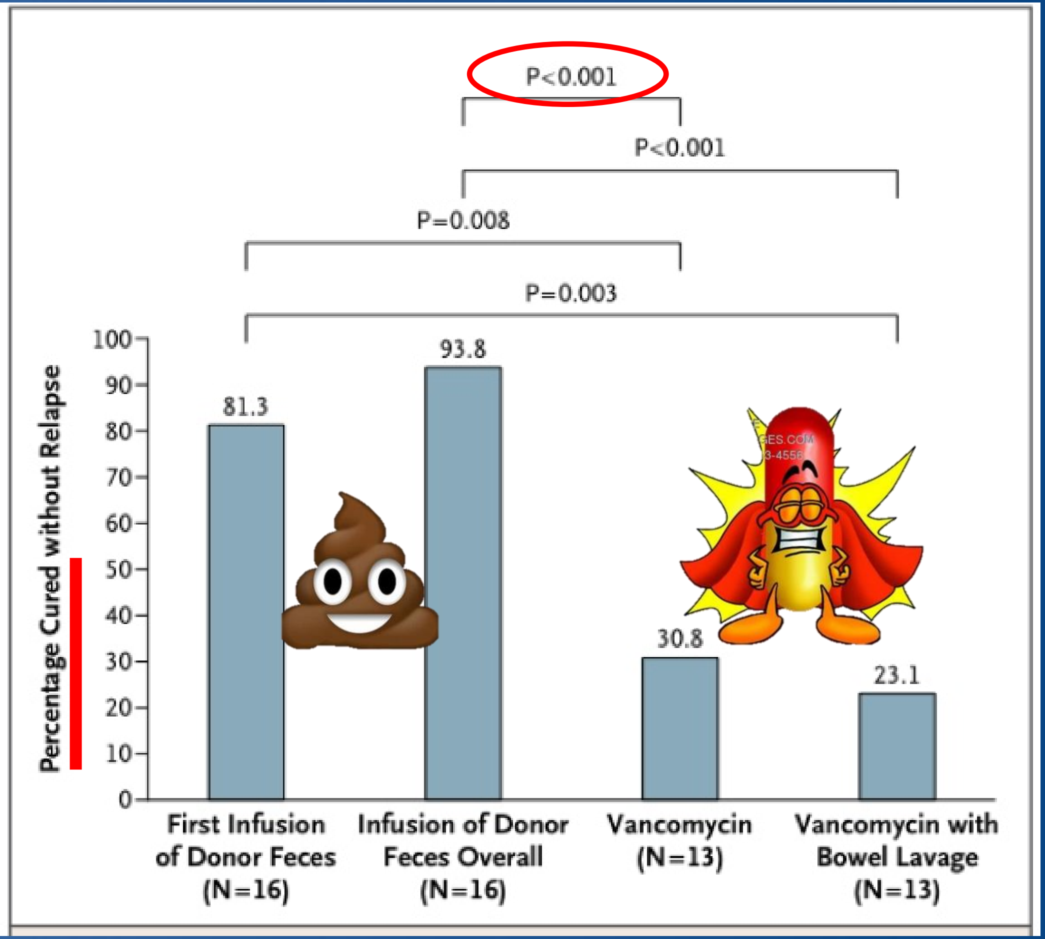
- Fulminant CDI
- Ulcerative colitis
- IBS constipation
- Metabolic syndrome
- Depression, chronic fatigue syndrome, MS

Photo from Science, 2009, 324:5931, pp. 1136 – 1137

# Fecal bacteriotherapy vs. vancomycin x 14 d for recurrent CDI

JOHNS HOPKINS MEDICINE

Proportions of patients who were cured by infusion of donor feces




Van Nood, E, et al. N Engl J Med 2013;368:407-15



## Fondo eterologo

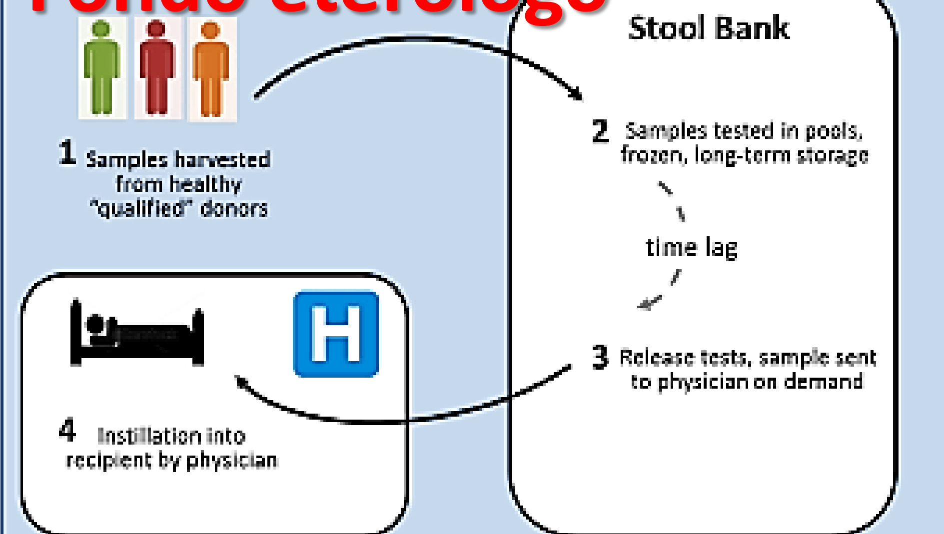



Figure 2: "Off-the-shelf" model

## Fondo autologo

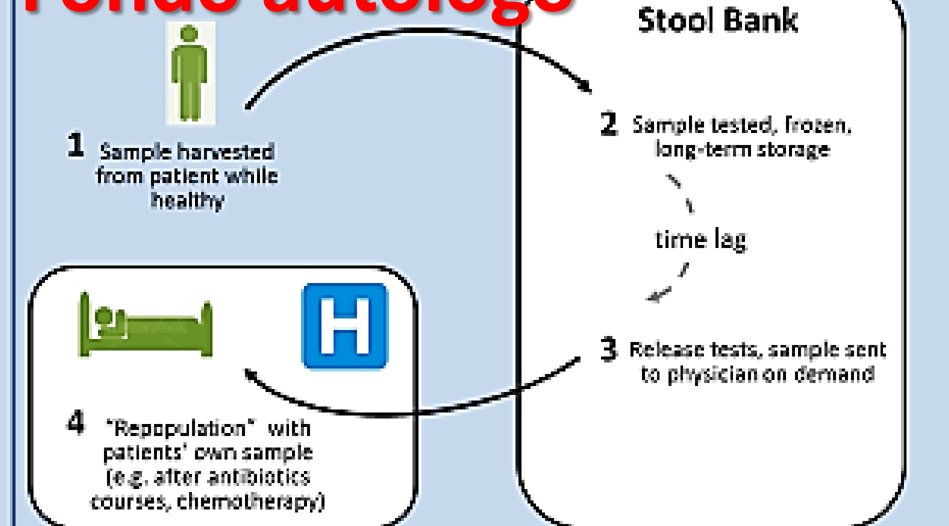



Figure 1c: Preemptive banking

# Altri usi vantaggiosi

Piero Manzoni (1933-1963)


**2012. N.Y.C. auction: 163.000 $**

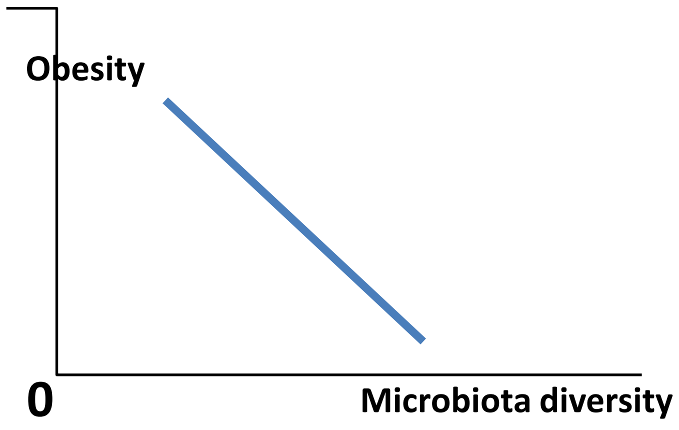
HMP

NIH

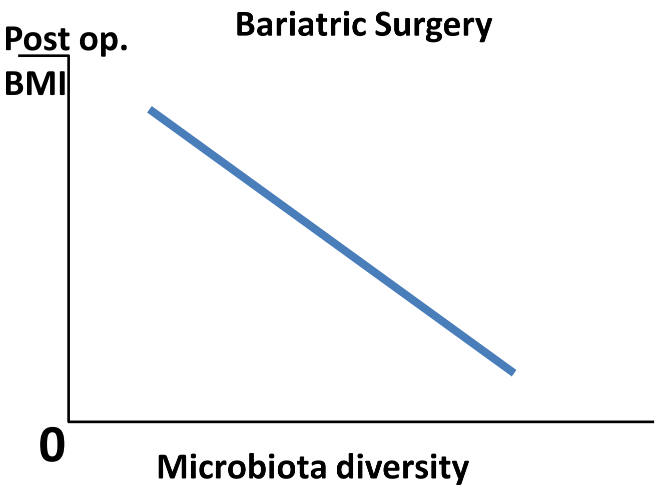
HUMAN MICROBIOTA PROJECT

# MICROBIOTA e CHIRURGIA

## Inverse correlation




Turnbaugh, 2008,2009




Cottillard 2012