Microbiota & Nutrizione

REGIONE DEL VENETO ULSS8 BERICA

Corso di formazione

RECENTI ACQUISIZIONI IN NUTRIZIONE CLINICA: RUOLO DEGLI AMBULATORI NUTRIZIONALI SIAN NELLA PREVENZIONE DELLE MALATTIE

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Azienda ULSS 8 – Vicenza

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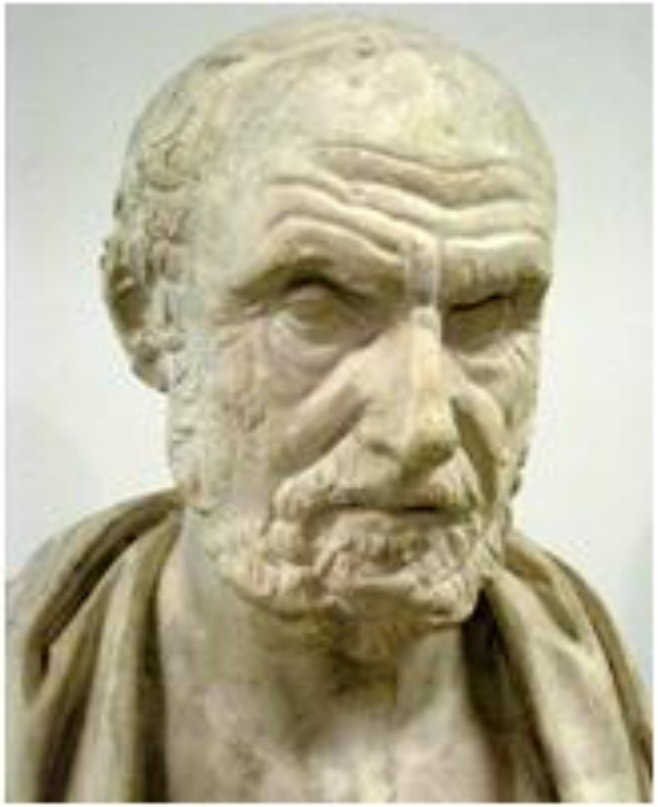
Obiettivi Formativi

- ☑ Definizione del microbioma /microbiota
- ☑ Ruolo metabolico del microbioma
- ☑ Modifiche mirate del microbioma
- ☑ Relazione con i nutrienti

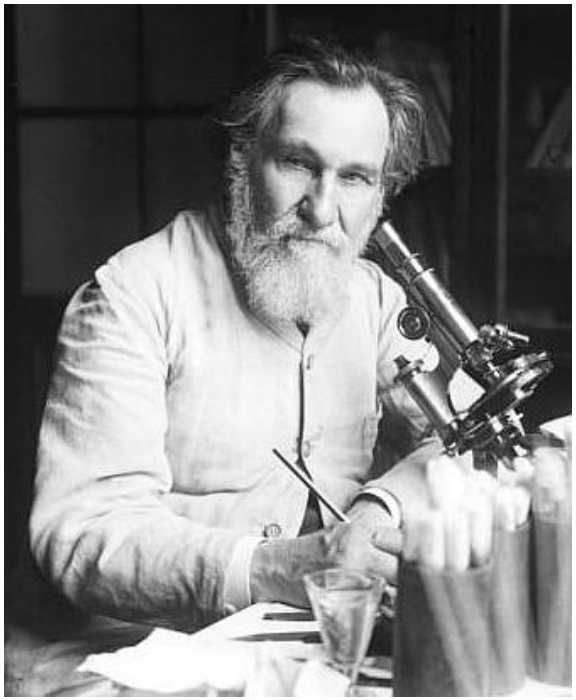
La storia...



- "... La morte risiede nell'intestino...."
- " ... La cattiva digestione è la radice di tutti i mali..."

Ippocrate di Cos 400 a.C.

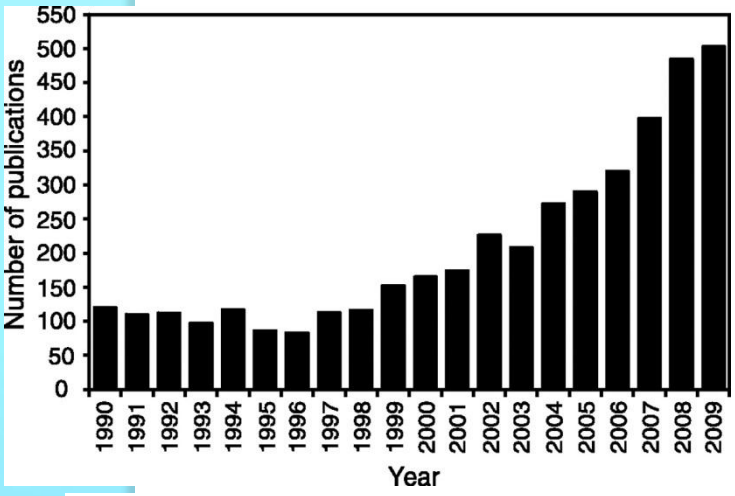
...Un nuovo punto di vista...



Ilya Ilich Metchnikoff
1907

Alfred Nissle
1917

n. Pubblicazioni : Microbiota
n. Studi clinici : Probiotici

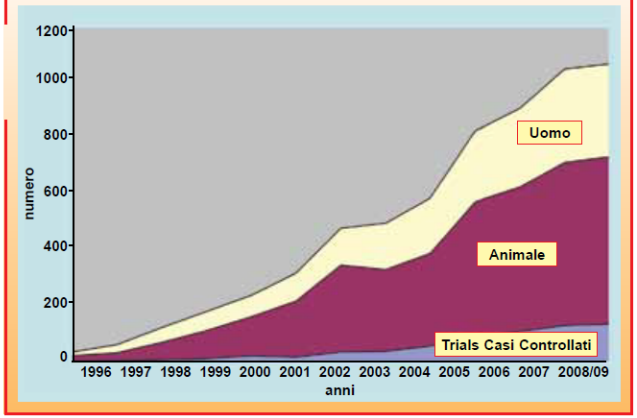


MICROBIOTA ***Pubmed :***

- ☑ ***intestinal microbiota,***
- ☑ ***gut microbiota,***
- ☑ ***intestinal flora,***
- ☑ ***gut flora,***
- ☑ ***intestinal microflora,***
- ☑ ***gut microflora***

Sekirov I, et al. 2010 Physiol Rev 90: 859–904

fig. 1: andamento numerico nel tempo e tipologia degli studi sui probiotici presenti su PubMed

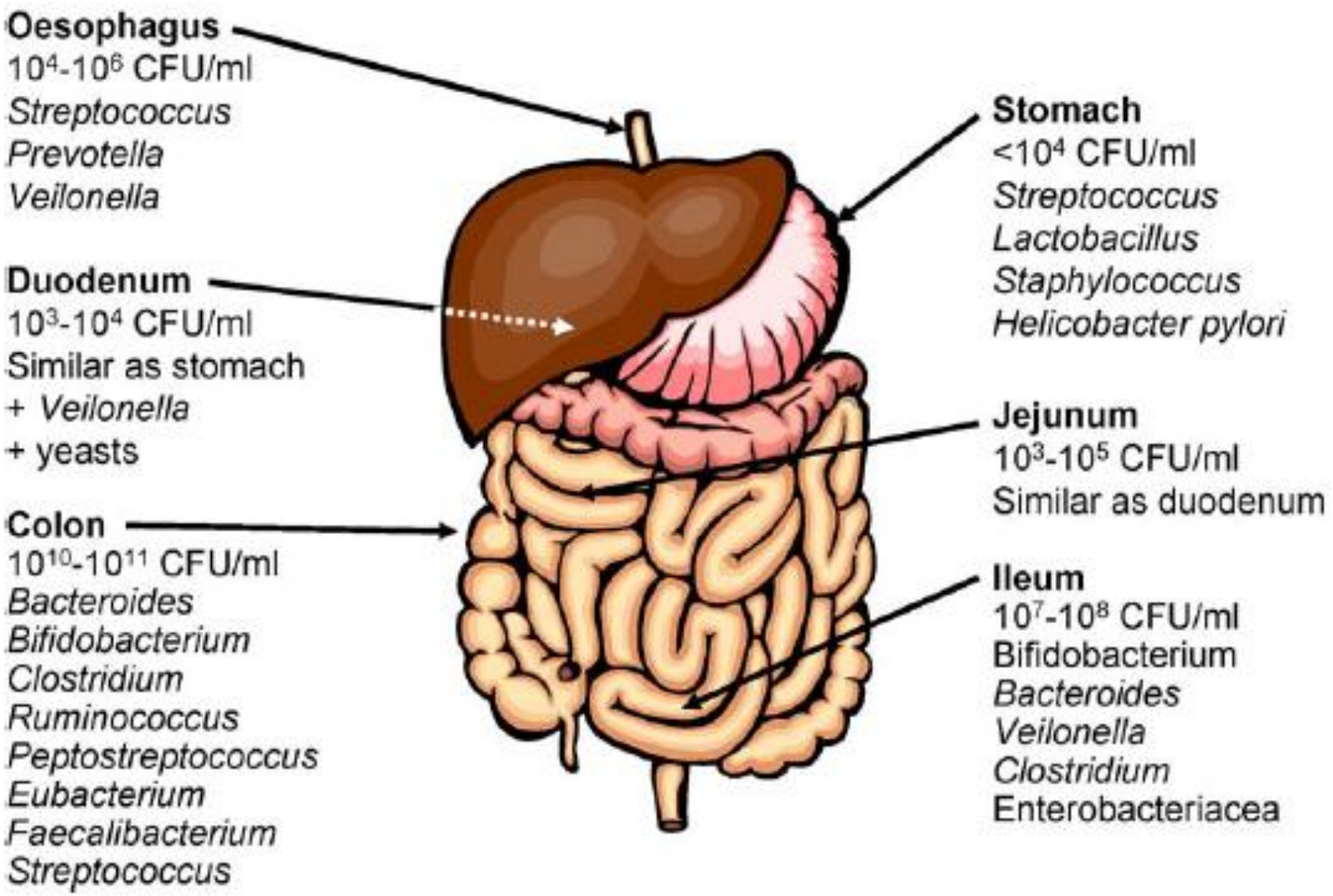


PROBIOTICI ***Pubmed :***

- ☑ ***Probiotic***
- ☑ ***Human and probiotic,***
- ☑ ***Probiotic therapy,***
- ☑ ***Probiotic CRT,***

Corleto et al. Giorn Ital End Dig 2011;34:191-195

K. Tiihonen et al. / Ageing Research Reviews 9 (2010) 107–116



MICROBIOTA

Batteri nell'intestino umano → 10^{14}
Cellule del corpo umano → 10^{13}
Migliaia di specie batteriche

MICROBIOMA (genoma batterico)

100 volte più geni rispetto al genoma umano

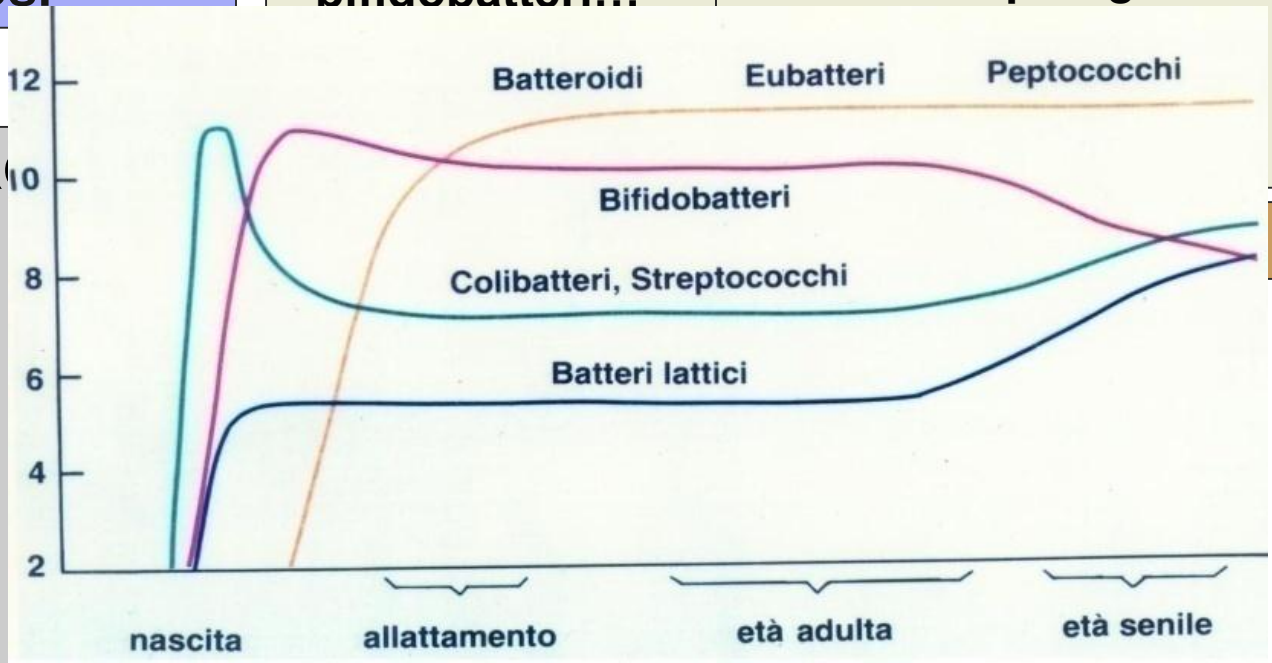
MICROBIOTA

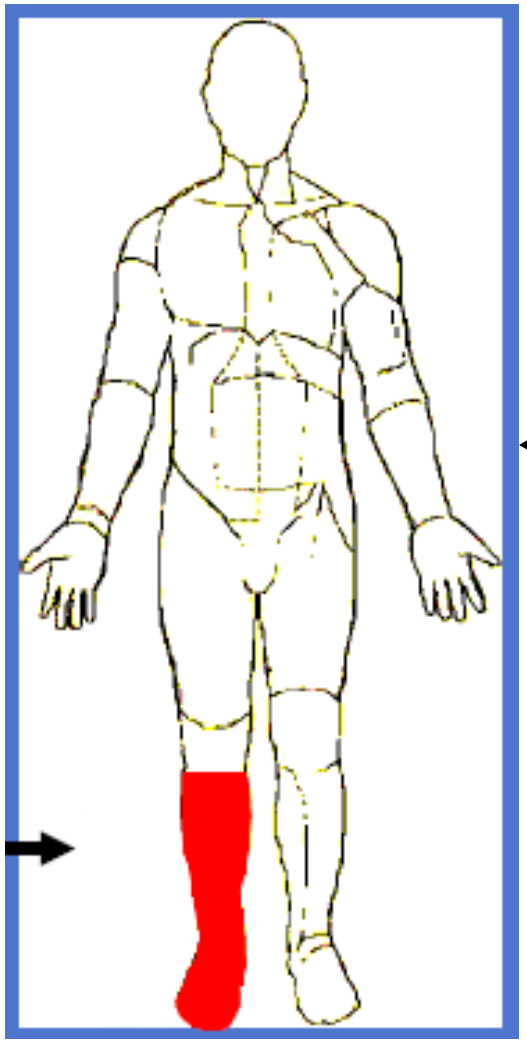
batteri con effetti favorevoli sull'ospite e batteri potenzialmente dannosi

FAVOREVOLI	POTENZIALMENTE DANNOSI
• lattobacilli • bifidobatteri…	•stafilococci • clostridi patogeni

COMPOSIZIONE MICR

- **genetica,**
- **microbiota materno,**
- **tipo di parto (naturale vs cesareo),**
- **tipo di allattamento (seno vs artificiale),**
- **Alimentazione,**
- **farmaci (antibiotici)**





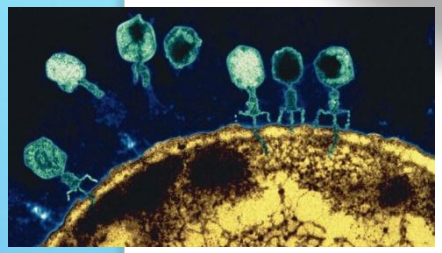
10^{14} Microbial cells

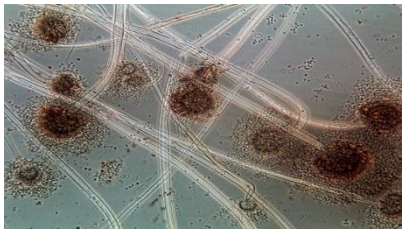
10^{13} Human cells

Martin J Blaser, 2013

Microbiota … o … Microbioma ?

Batterioma
Vironma
Micetoma
Altro…oma





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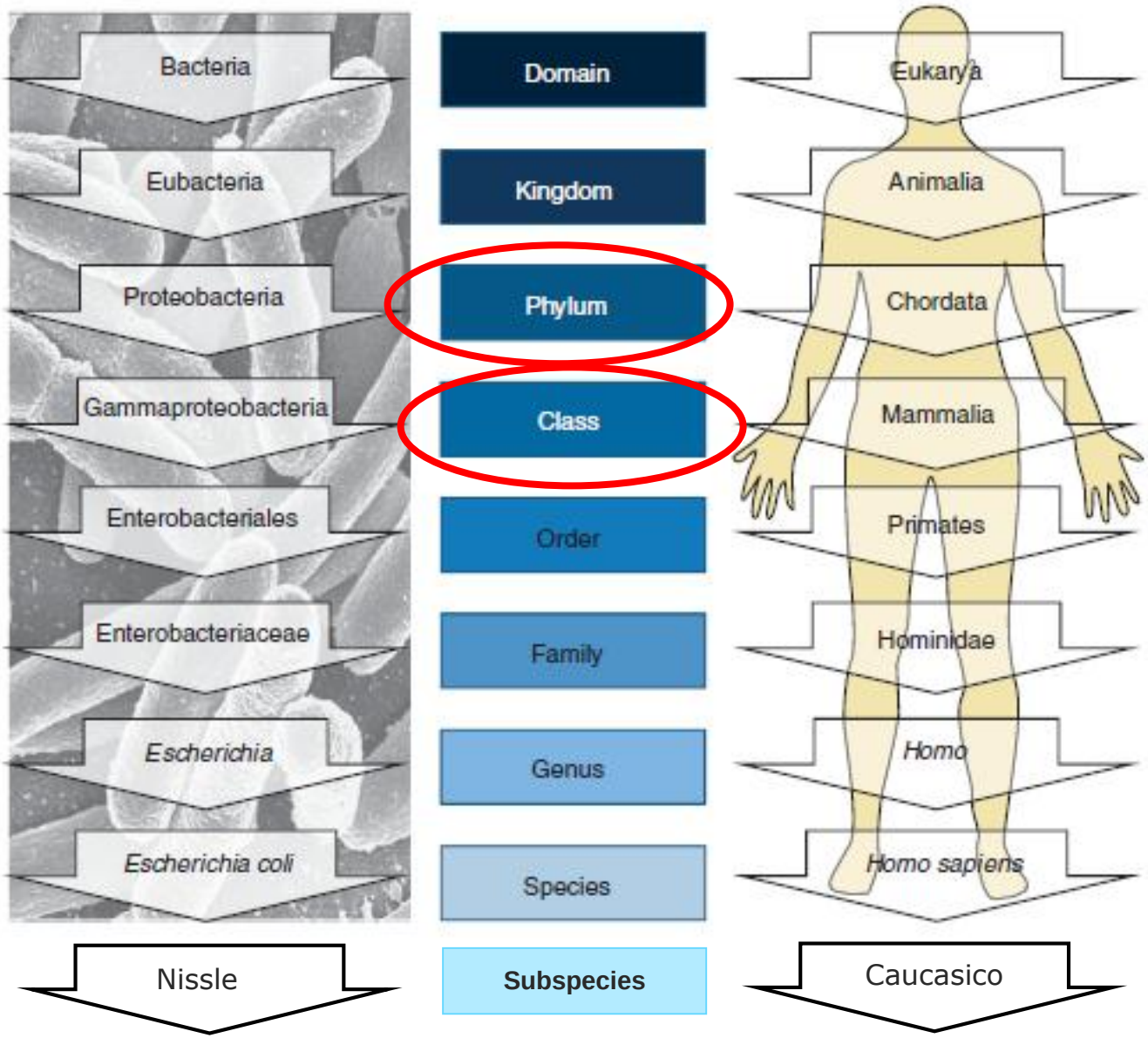
Tyler et al. (modificato) - Am J Gastroent, 2014; 109:983



A map of diversity in the human microbiome

Streptococcus dominates the oral cavity with *S. mitis* > 75% in the cheek

Propionibacterium acnes lives on the skin and nose of most people

Many *Corynebacterium* species characterize different body sites:
C. matruchoti the plaque
C. accolens the nose
C. croppenstedtii the skin

Lactobacillus species (*L. gasseri*, *L. jensenii*, *L. crispatus*, *L. iners*) are predominant but mutually exclusive in the vagina

Staphylococcus epidermidis colonizes external body sites

Several *Prevotella* species are present in the gastrointestinal tract. *P. copri* is present in 19% of the subjects and dominates the intestinal flora when present

Bacteroides is the most abundant genus in the gut of almost all healthy subjects

Campylobacter includes opportunistic pathogens, but members live in the oral cavities of most healthy people in the cohort

E. coli is present in the gut of the majority of healthy subjects but at very low abundance

Commensal microbes

Potential pathogens

The four most abundant phyla

- Actinobacteria
- Bacteroidetes
- Firmicutes
- Proteobacteria

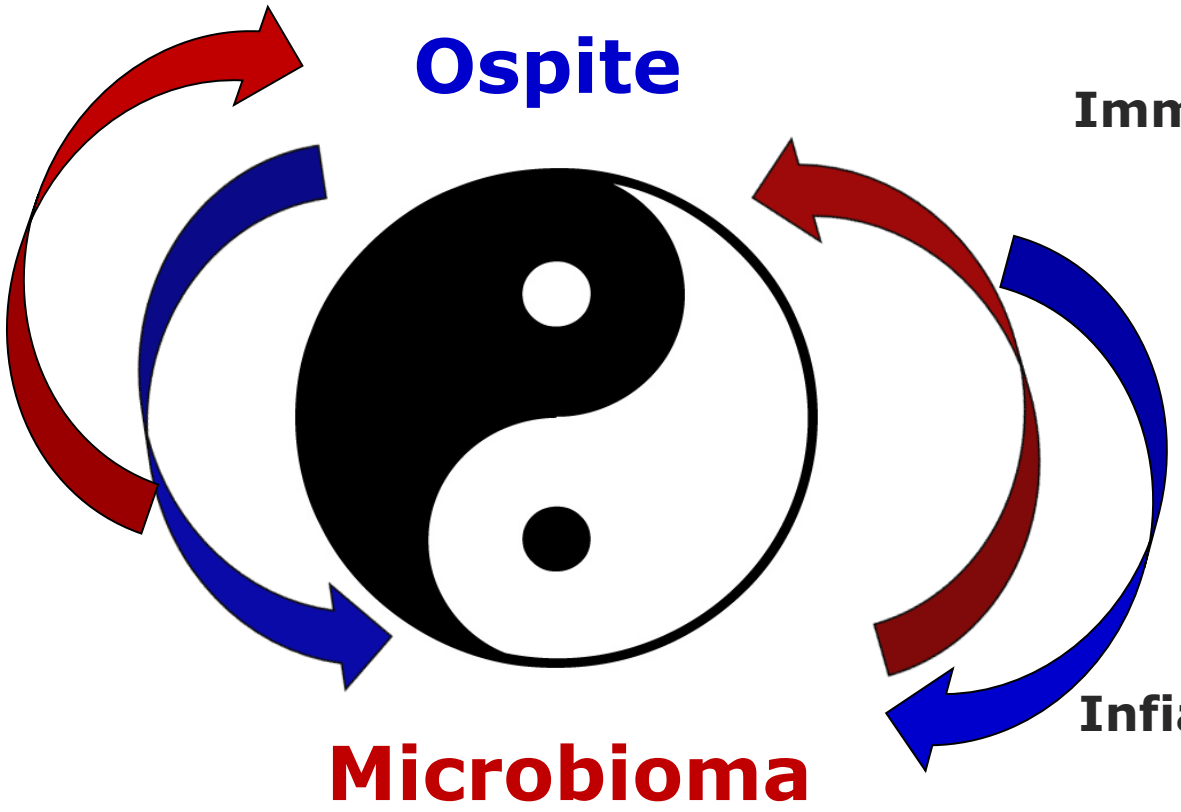
Low abundance phyla

- Chloroflexi
- Cyanobacteria
- Euryarchaeota
- Fusobacteria
- Lentisphaerae
- Spirochaetes
- Synergistetes
- Tenericutes
- Thermi
- Verrucomicrobia

National Institutes of Health Human Microbiome Project

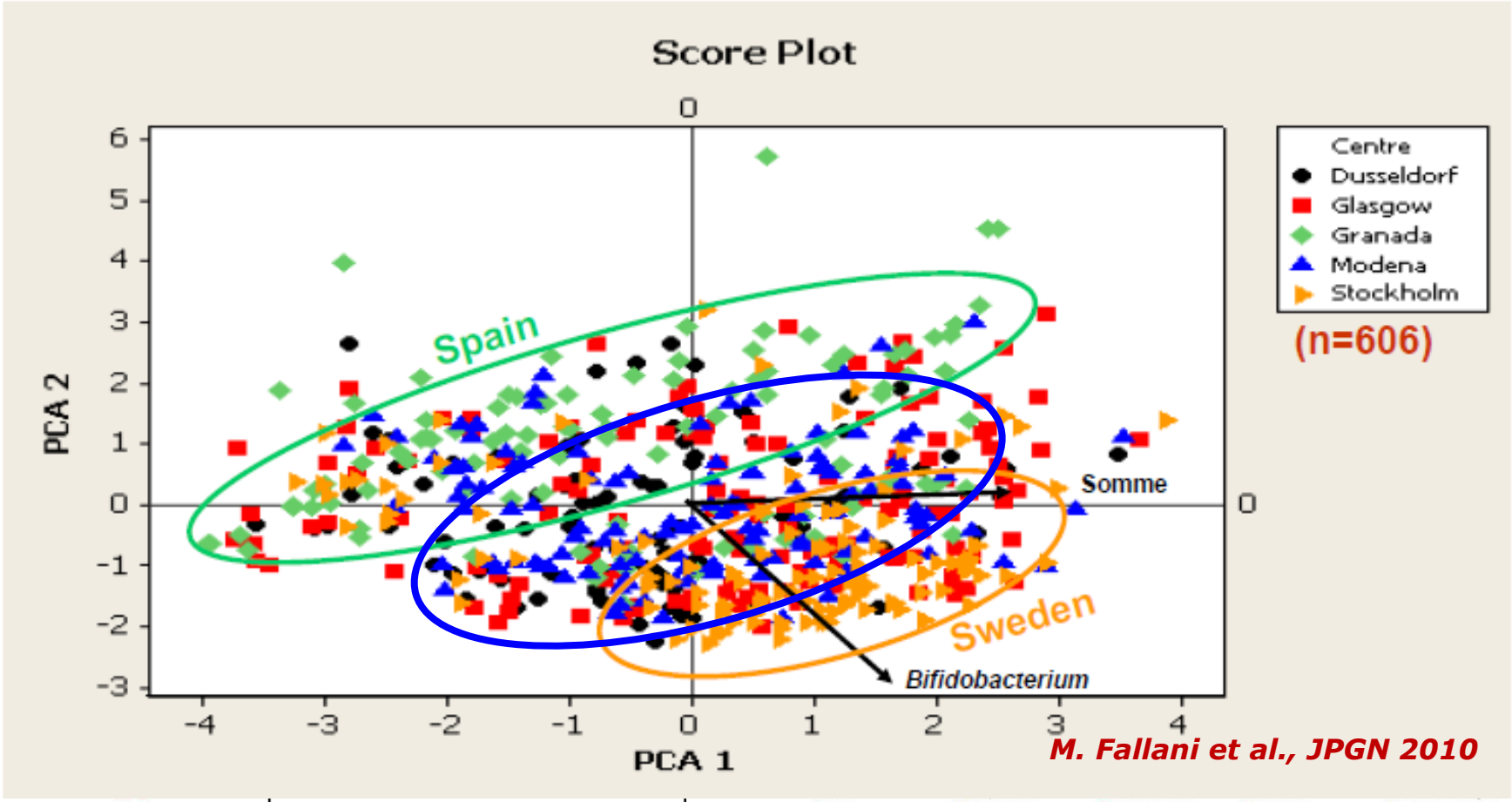
N. Segata & C. Huttenhower
http://huttenhower.sph.harvard.edu

Interazione



Numerosità, Complessità, variabilità, differenze …

Fecal microbiota of 6 weeks-old European infants

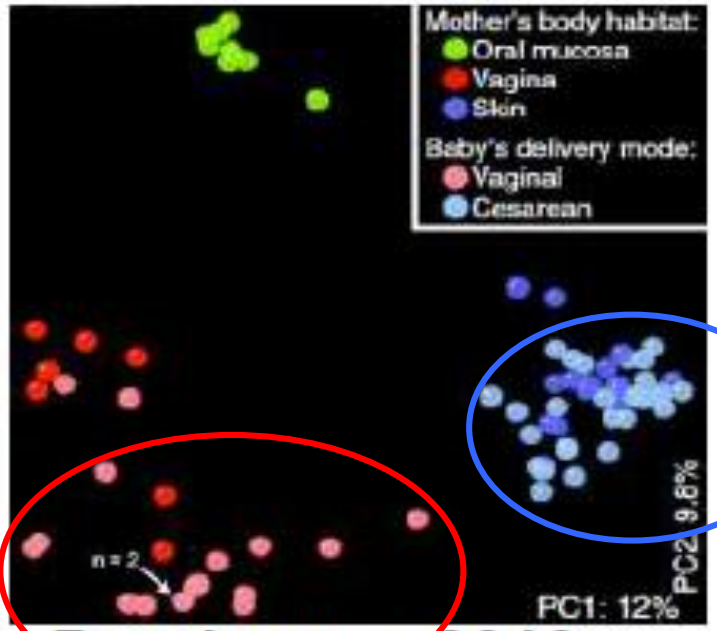


M. Fallani et al., JPGN 2010

Enterococcus Raoultella Salmonella Enterobacter Klebsiella
Citrobacter Propionibacterium Others No hits

Kurokawa K et al. DNA Res 2007;14:169-181

The structure of the human intestinal microbiota across the life cycle.

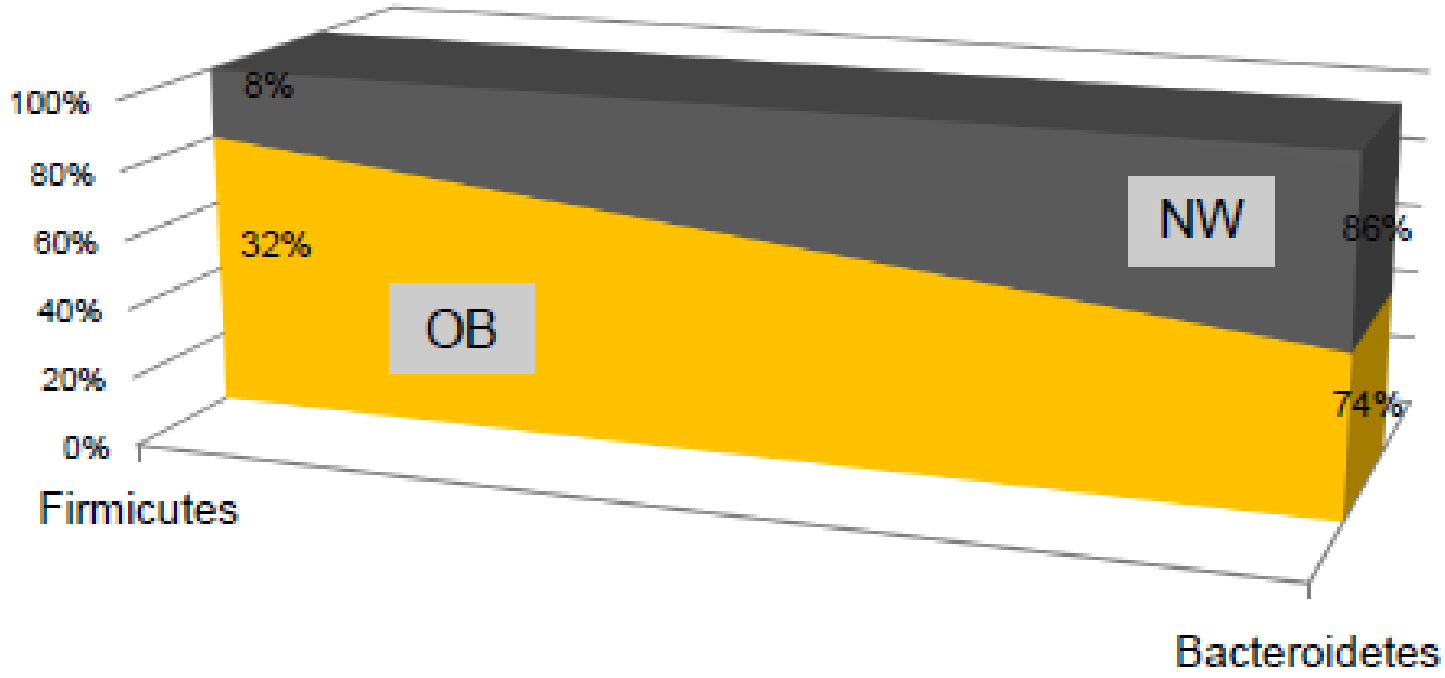


Parto cesareo

Parto per via vaginale

Dominguez 2010

Bacteroidetes
Firmicutes
Actinobacteria
Proteobacteria
variable/other

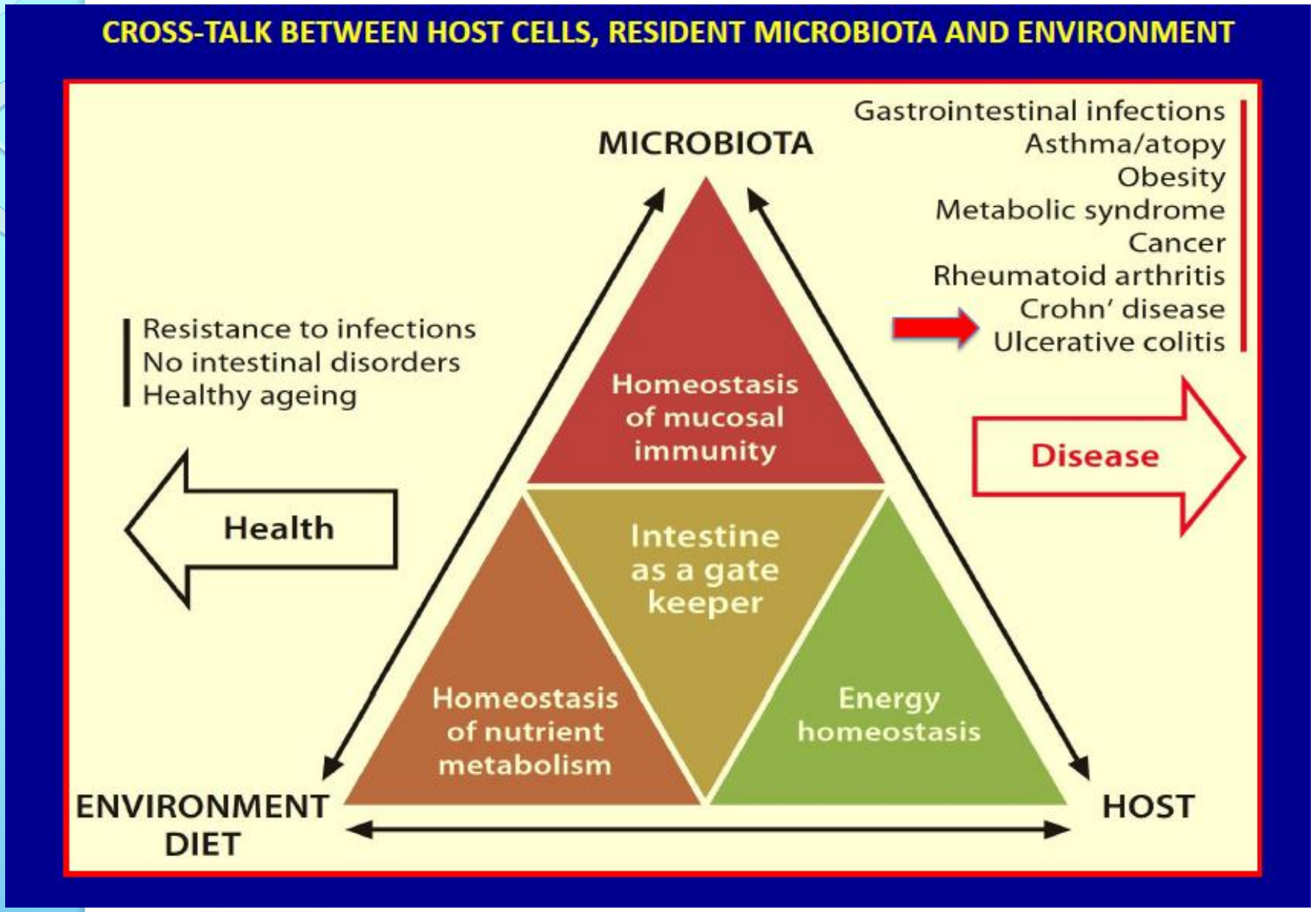

100%
80%
60%
40%
20%
0%
8%
32%
NW
OB
86%
74%
Firmicutes
Bacteroidetes

Funzioni microbioma

- ☑ ***Protettive:***
  antibatterici
  competizione batt.
  barriera intestinale
  immunità locale
  anticarcinogenesi
  infiammazione
- ☑ ***Nutritive:***
  vitamine (B e K)
  fatt. crescita epitelio
- ☑ ***Controllo Motilità***
- ☑ ***Controllo Secrezione***
- ☑ ***Percezione Dolore***
- ☑ ***Sintesi Neurotrasmettitori:***
  GABA
  Melatonina
- ☑ ***Sintesi Ormoni :***
  istamina
  acetilcolina
  dopamina, ecc.
- ☑ ***Regolazione metabolismo:***
  farmaci
  obesità
- ☑ ***Regolazione tono umore***
- ☑ ***Comportamento alimentare***


Modulazione dei geni dell'ospite
Sintesi sostanze per recettori
Sintesi sostanze regolatrici
Interazione sistema Immunitario enterico
Sintesi Nutrienti
Antagonismo
Competizione
Simbiosi
2010
Glicemia
2000
Vie di stoccaggio del grasso
1917
1900
Digestione

Gut bacteria	Level change	Health effect
		Immunological dysfunction
		Type 2 diabetes
Bacteroides, *Proteobacteria*	High	
Firmicutes, ***Clostridium***, ***Bifidobacterium***	Low	
		Inflammatory bowel disease (IBD)
Sulphate-reducing bacteria, *Escherichia coli*	High	
Clostridium IXa, IV (*F. prausnitzii*) groups, ***Bacteroides***, ***Bifidobacterium***	Low	
		Ulcerative colitis pouchitis (a form of IBD)
Clostrudium, *Eubacterium*, *Firmicutes*, *Verrucomicrobia*	High	
Lactobacillus, *Streptococcus*, ***Bacteroides***, *Proteobacteria*	Low	
		Crohn's disease (a form of IBD)
Bacteroides vulgates, *Enterbacteriaceae*, *Escherichia coli*, *Klebsiella pneumonia* and *Streptococcus viridians*	High	
Lactobacillus, ***Bifidobacterium***	Low	
		Coeliac disease
Bacteroides-Prevotella; *Escherichia coli*, *Klebsiella pneumonia* and *Streptococcus viridans*	High	
Bifidobacterium, ***Clostridium histolyticum***, ***C. lituseburense***, *F. prausnitzii*	Low	
		Rheumatoid arthritis
Segmented filamentous bacteria	High	
Bifidobacteria, ***Bacteroides-Prevotella*** group,	Low	
Bacteroides fragilis subgroup, *E. rectale-C. coccoides* group		
		Autism
Clostridium histolyticum gp (*Clostridium cluster* I & II), ***Bacteroides***	High	
Bifidobacterium	Low	
		Obesity/ Metabolic disorder
Lactobacillus, *Faecalibacterium prausnitzii*, *Staphylococcus aurus* *Methanobrevibacter smithii*, *Prevotella*	High	
Bacteroides, Sulphate-reducing bacteria, ***Bifidobacteria***	Low	
		Anorexia nervosa
Methanobrevibacter smithii	High	
		Metabolic dysfunction
		Colorectal cancer/ adenomatous polyposis
B. fragilis, ***B. thetaiotaomicron***, ***B. Ovatus***, ***B. uniformis*** , ***Clostridium leptum***, ***C. coccoides*** subgroups, *Enterobacteriaceae*, *Enterococcus fecalis*	High	
Bifidobacterium	Low	

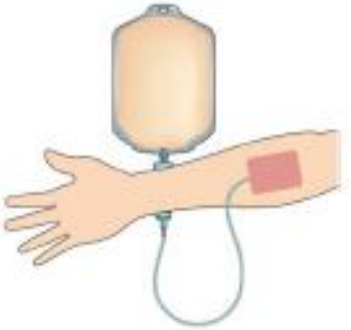

CROSS-TALK BETWEEN HOST CELLS, RESIDENT MICROBIOTA AND ENVIRONMENT
MICROBIOTA
Gastrointestinal infections
Asthma/atopy
Obesity
Metabolic syndrome
Cancer
Rheumatoid arthritis
Crohn' disease
Ulcerative colitis
Resistance to infections
No intestinal disorders
Healthy ageing
Homeostasis of mucosal immunity
Disease
Health
Intestine as a gate keeper
Homeostasis of nutrient metabolism
Energy homeostasis
ENVIRONMENT
DIET
HOST

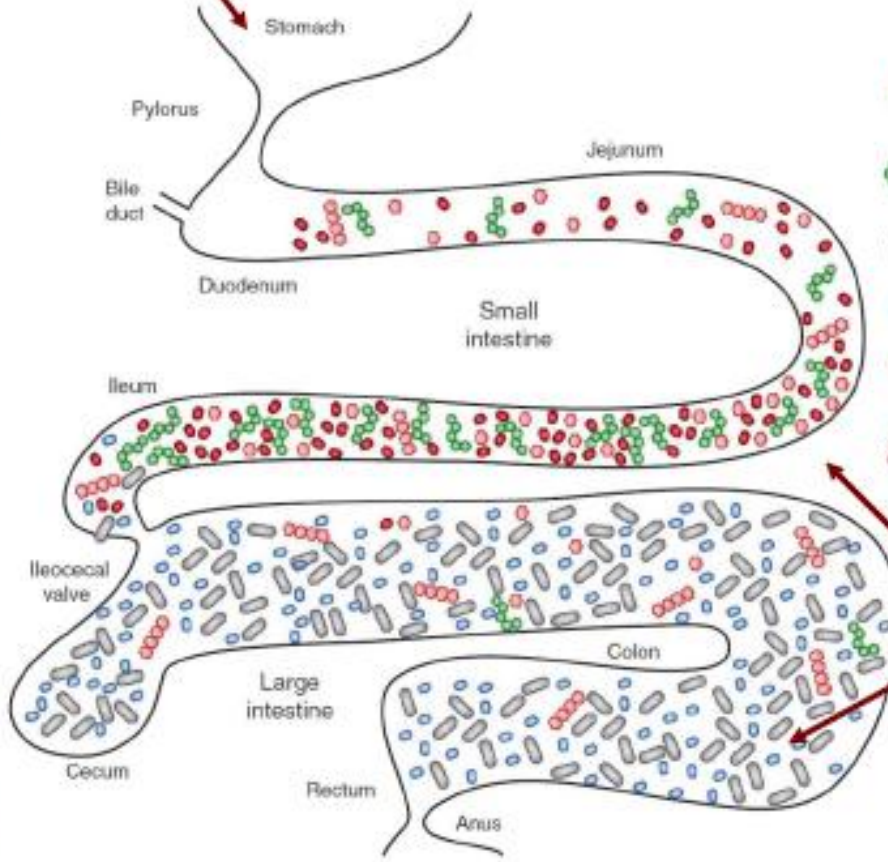
The Gut: A highly evolved and balanced ecosystem

Nutrients "IN"

+

Antibiotic exposure- an unavoidable side effect of human progress





>20 M length
200M² in surface area

Effect of Nutrients/Abx on microbiota?

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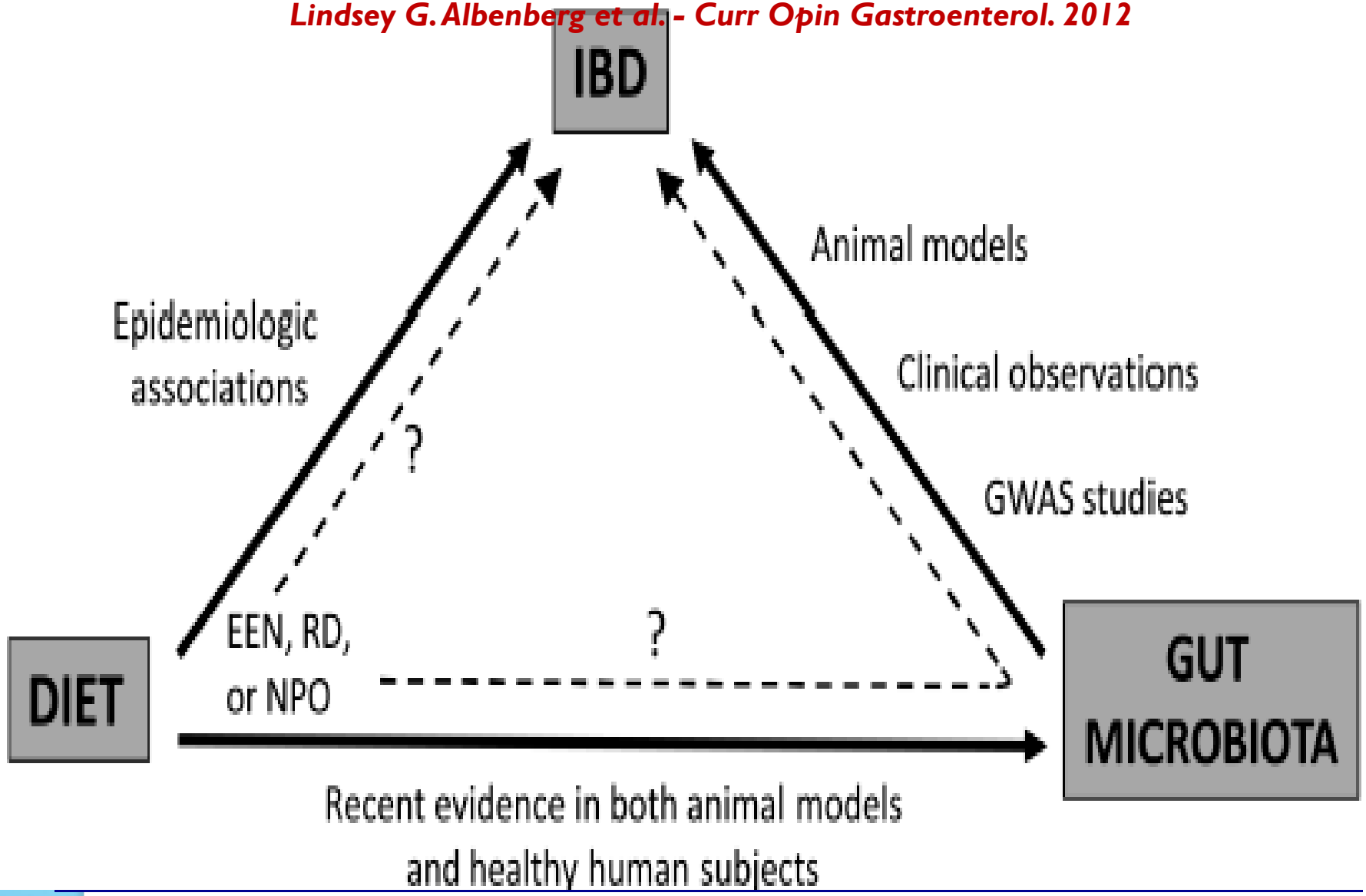
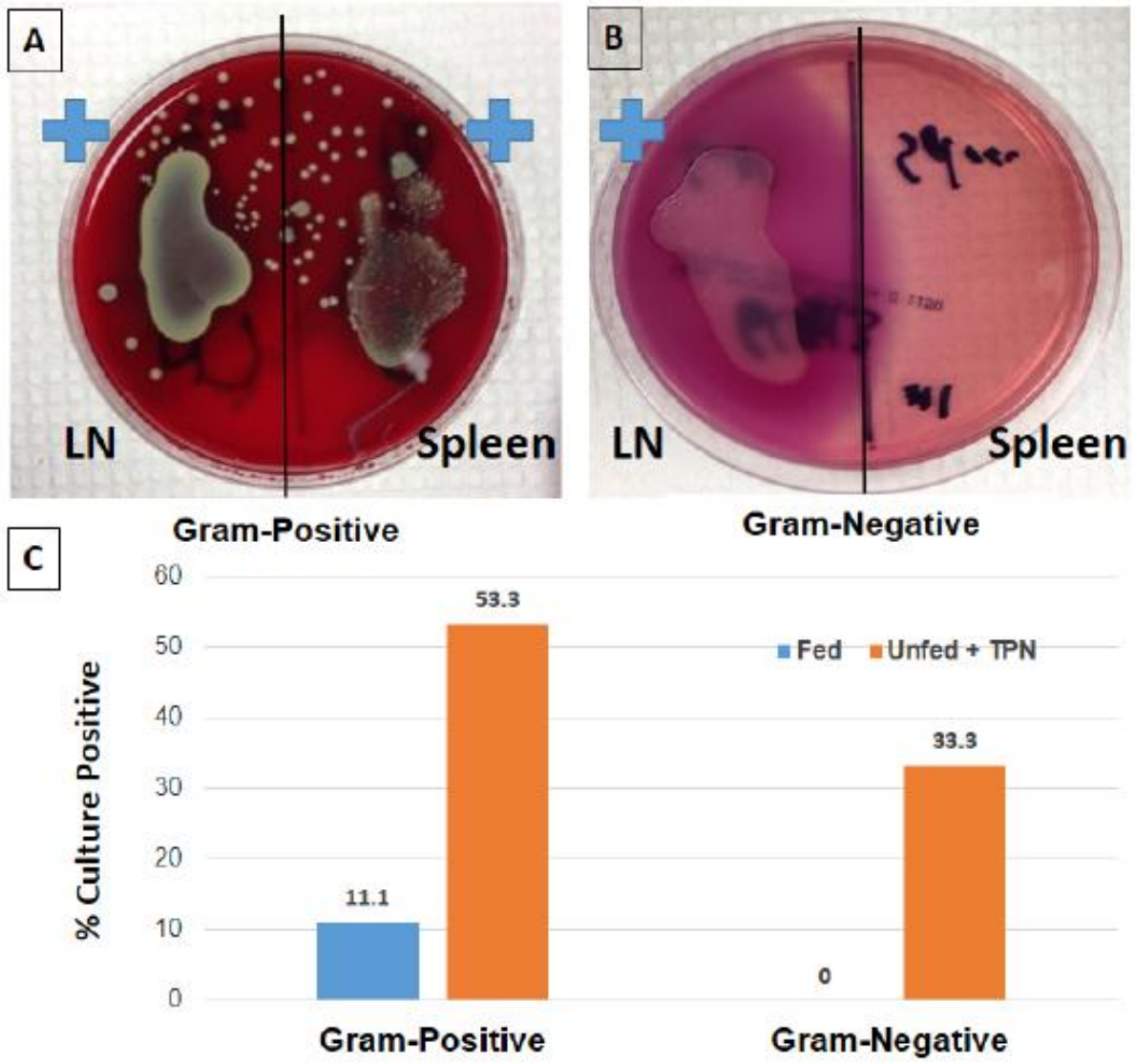
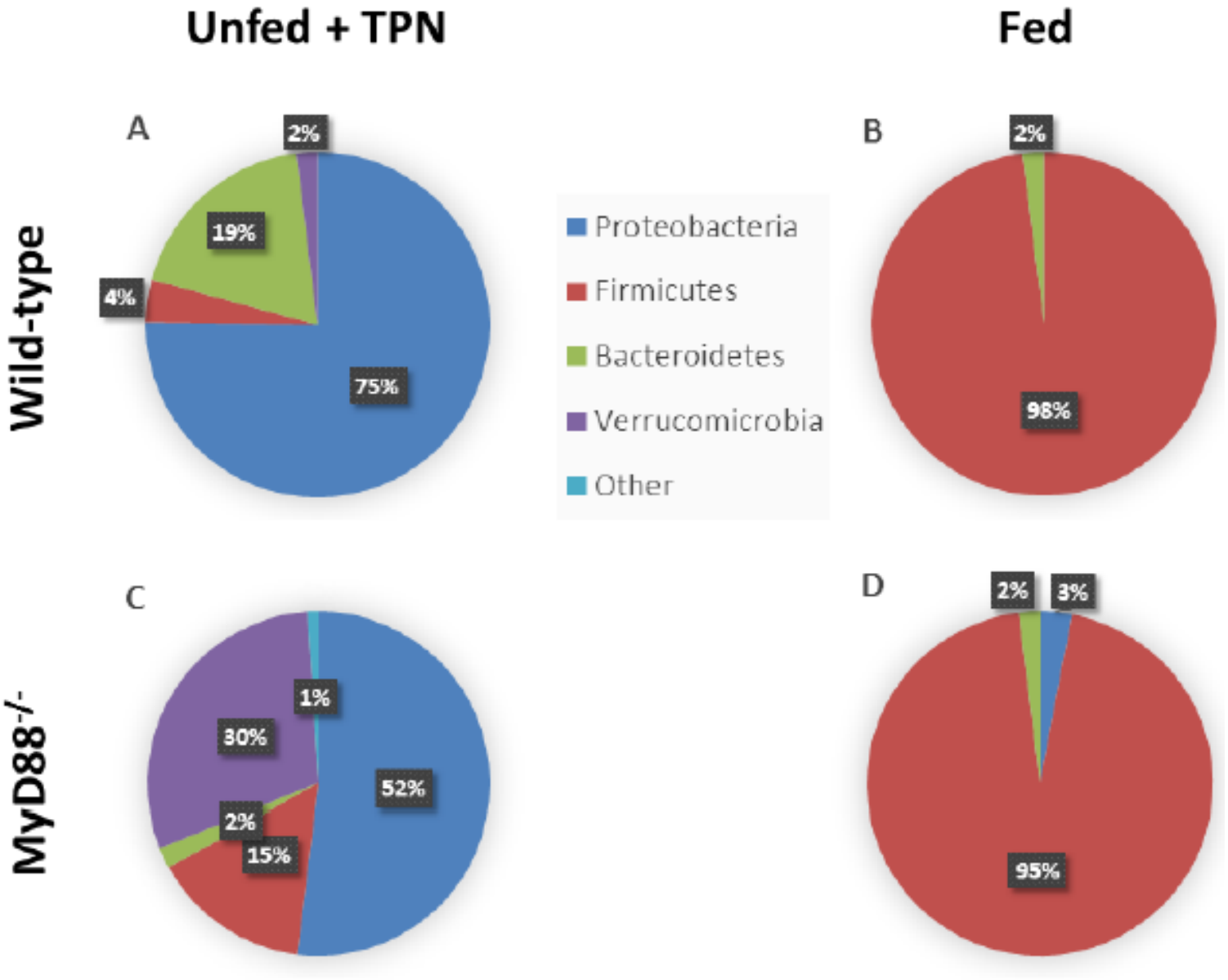
Lindsey G. Albenberg et al. - Curr Opin Gastroenterol. 2012



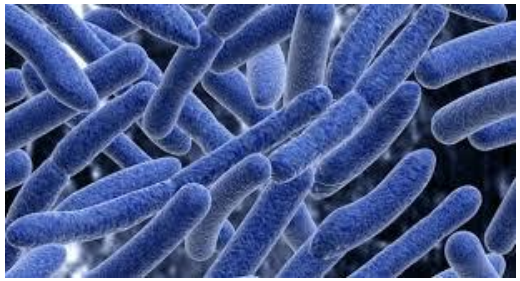
FR. Demehri, MBarrett, MW. Ralls, et al. Frontiers in Cellular and Infection Microbiology 2013



FR. Demehri, MBarrett, MW. Ralls, et al. Frontiers in Cellular and Infection Microbiology 2013

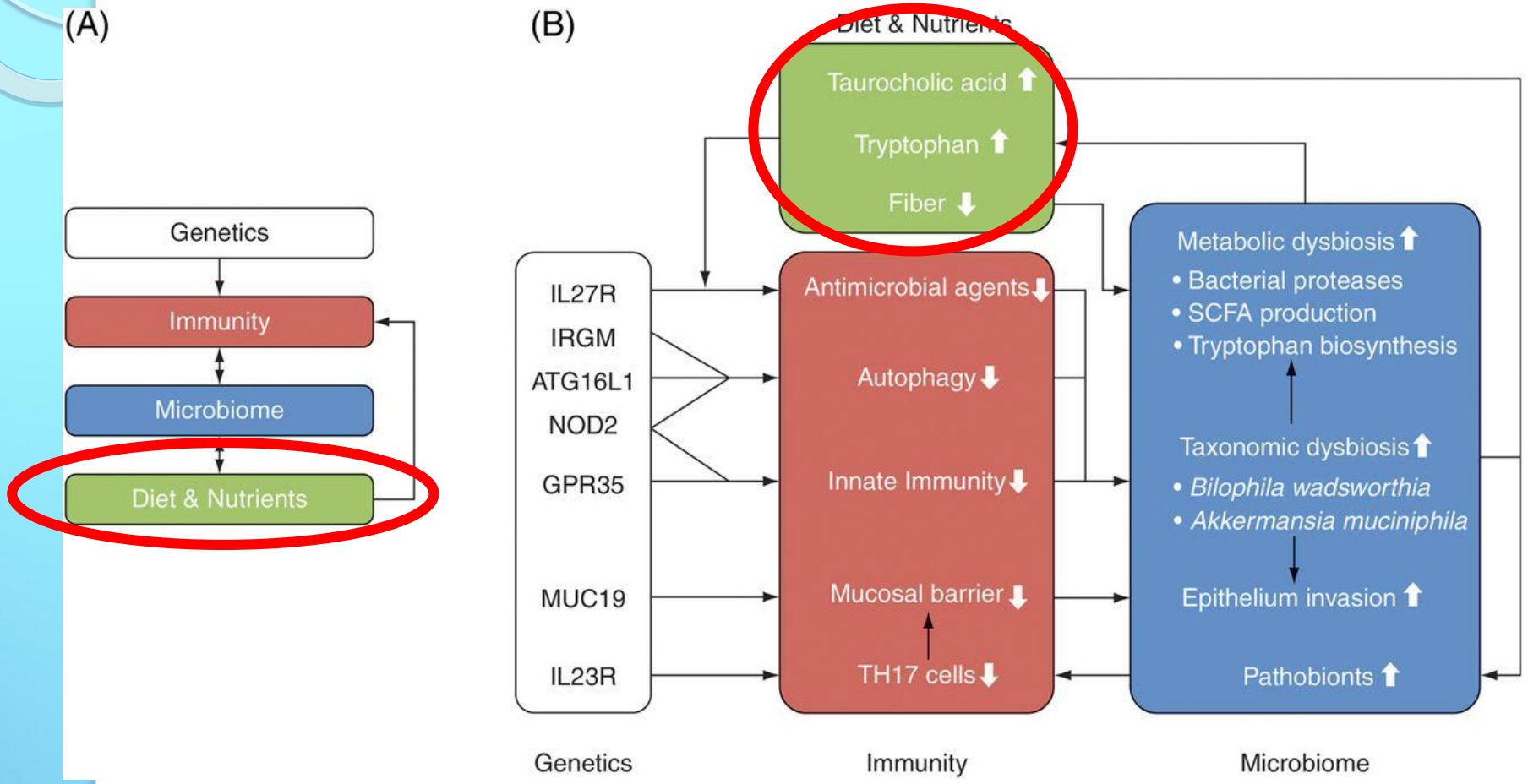


Microbiota intestinale

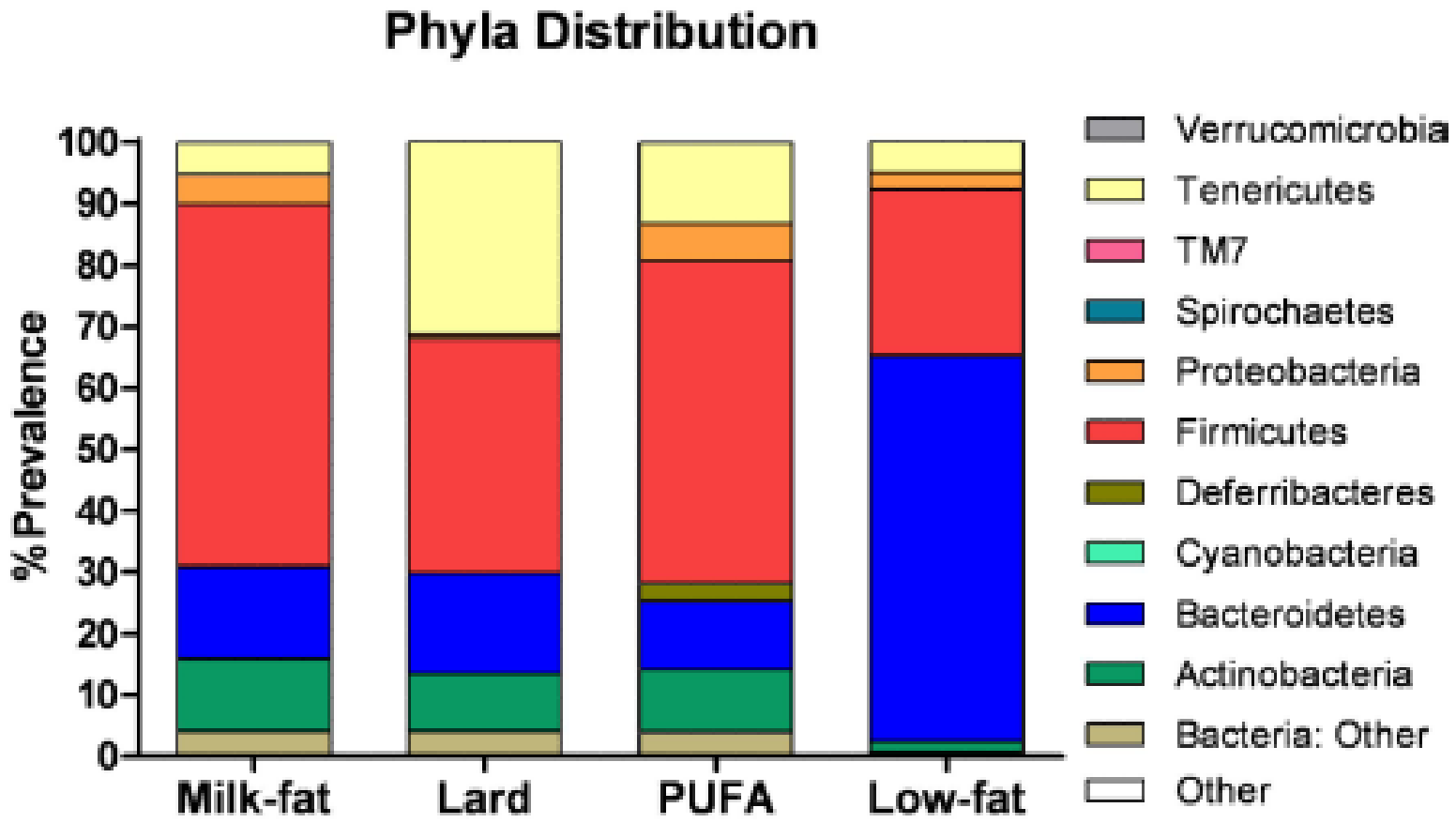


Nutrienti

Interaction network of host genetics, the gut microbiome and diet in overview (A) and in detail (B)



Dan Knights et al. Gut 2013;62:1505-1510



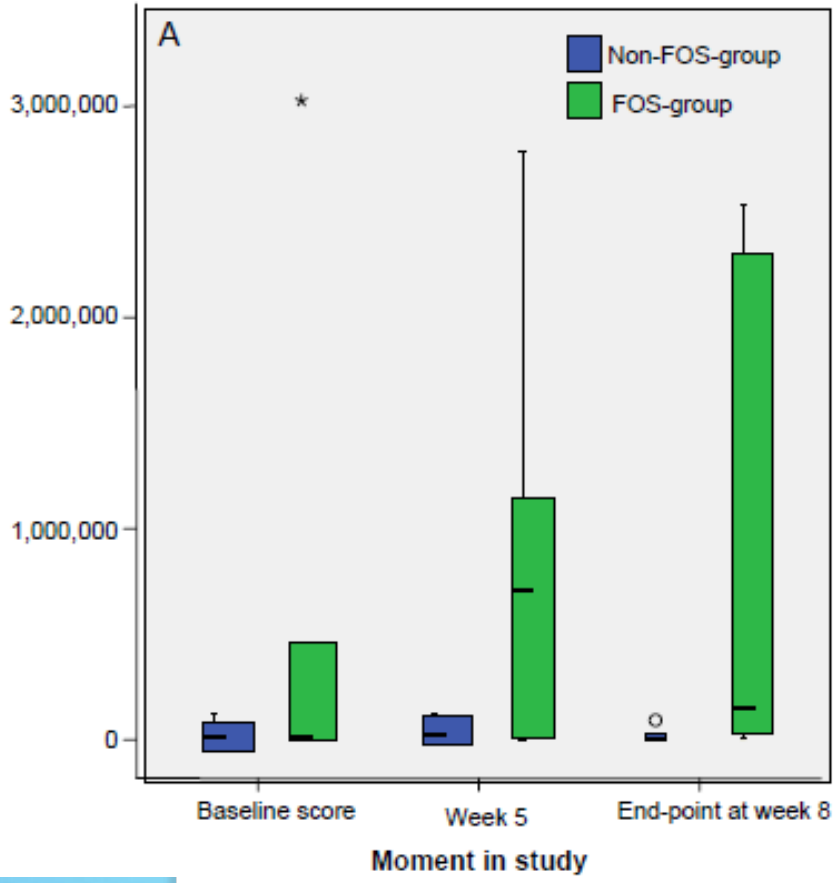
Edmond Huang, MS. et al. - JPEN J Parenter Enteral Nutr. 2013 ; 37(6)

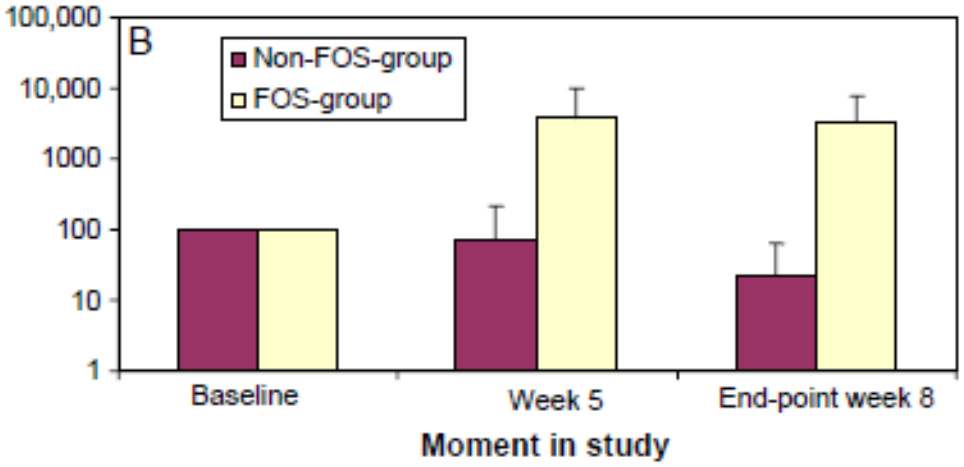
Table 1 *E cloacae* colonization with various formula diets

	NAN	Acidified NAN	Pelargon	NAN with probiotic	P^a
Lungs	27/35 (77%)	19/27 (70%)	10/33 (30%)	3/33 (9%)	<.001
Liver	11/35 (31%)	6/27 (22%)	10/33 (30%)	1/33 (3%)	<.025
Spleen	8/35 (23%)	7/27 (26%)	10/33 (30%)	1/33 (3%)	<.05
MLN	9/35 (26%)	11/27 (41%)	10/33 (30%)	3/33 (9%)	<.05
Stomach	28/35 (80%)	21/27 (78%)	15/33 (45%)	5/33 (15%)	<.001
Cecum	35/35 (100%)	27/27 (100%)	33/33 (100%)	21/33 (64%)	<.001

[a] Probiotic diet group compared with all other groups.

MR. McVay, C Boneti, CM. Habib et al. - Journal of Pediatric Surgery (2008) 43, 25–29





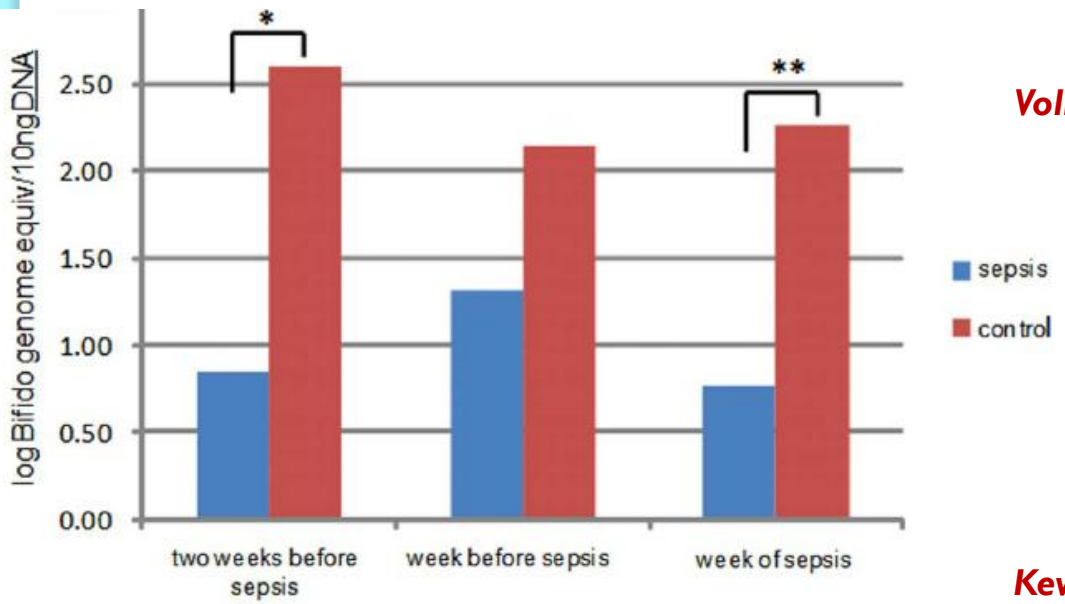
N J. Wierdsma et al. - Scandinavian Journal of Gastroenterology 2009, 19,

Kentaro Shimizu, Hiroshi Ogura, Takashi Asahara et al. _Digestive Disease and Science 2013,

Fecal flora	SIRS patients	Normal
Total obligate anaerobes	8.3 ± 2.3*	10.5 ± 0.5
Bacteroidaceae	7.3 ± 3.0*	10.1 ± 0.4
Bifidobacterium	4.8 ± 3.3*	9.6 ± 0.7
Clostridium	2.1 ± 1.0	2.1 ± 0.7
Veillonella	3.1 ± 1.8*	7.0 ± 1.2
Total facultative anaerobes	7.8 ± 1.4	7.5 ± 0.4
Lactobacillus	2.7 ± 1.5*	5.0 ± 1.0
Enterobacteriaceae	4.1 ± 2.7*	7.4 ± 0.8
Enterococcus	6.4 ± 2.5	7.0 ± 0.9
Staphylococcus	5.3 ± 1.7*	2.7 ± 0.8
Pseudomonas	2.8 ± 1.4*	ND
Candida	2.5 ± 1.0	2.0 ± 0.5

Kentaro Shimizu, Hiroshi Ogura, Takashi Asahara et al. _Digestive Disease and Science 2013,

Organic acids	SIRS patients	Normal
Total organic acid	30.3 ± 20.3*	88.4 ± 21.2
Succinic acid	2.0 ± 2.5	0.9 ± 1.2
Lactic acid	3.8 ± 5.5	0.5 ± 0.3
Formic acid	1.7 ± 2.9	0.4 ± 0.3
Acetic acid	18.7 ± 15.9*	50.8 ± 13.1
Propionic acid	2.5 ± 4.6*	18.7 ± 6.8
Isobutyric acid	0.1 ± 0.5	1.1 ± 0.3
Butyric acid	0.9 ± 2.3*	16.6 ± 6.7
Isovaleric acid	0.5 ± 1.9	1.4 ± 0.7
Valeric acid	0.1 ± 0.7	0.6 ± 0.4
pH	7.4 ± 0.6*	6.6 ± 0.3



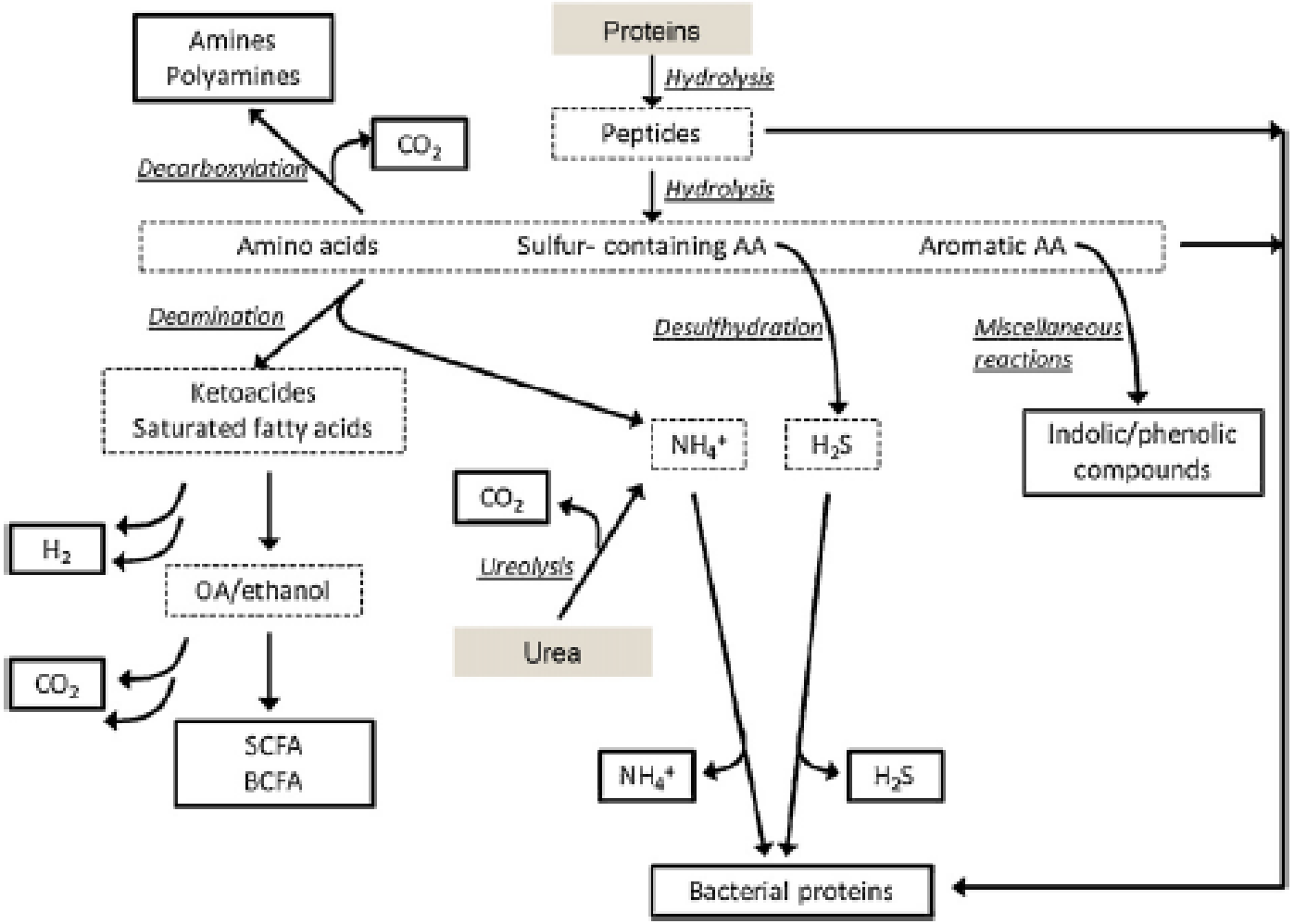
Volker Mai et al. - PLOS ONE 2013

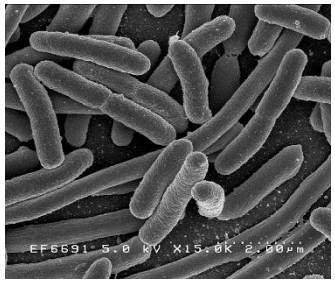
Kevin Whelan et al. Am J Clin Nutr 2009

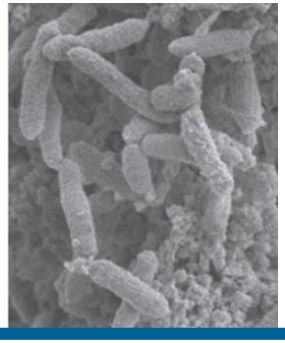
	Start (days 1–4)	Middle (days 6–9)	End (days 11–14)	*P* value[1]
Microbiota, $n = 20$ (log_{10}/g dry feces)[2]				
Bifidobacteria				
No diarrhea	9.4 ± 1.0[3]	9.4 ± 1.2	9.4 ± 1.4	0.069
Diarrhea	8.7 ± 0.6	8.7 ± 0.8	8.5 ± 0.6	
Clostridia				
No diarrhea	9.7 ± 0.6	9.7 ± 0.6	9.8 ± 0.5	0.026
Diarrhea	10.1 ± 0.6	10.2 ± 0.5	10.0 ± 0.5	
Microbiota, $n = 20$ (% of total)[2]				
Bifidobacteria				
No diarrhea	4.3 ± 5.1	9.3 ± 16.0	12.2 ± 18.3	0.029
Diarrhea	0.6 ± 0.5	1.7 ± 3.2	0.4 ± 0.3	
Bacteroides-prevotella				
No diarrhea	9.5 ± 8.5	7.5 ± 8.0	4.0 ± 4.7	0.070
Diarrhea	13.4 ± 17.7	12.2 ± 8.3	12.7 ± 9.3	

… e le proteine …

A.-M. Davila et al. - Pharmacological Research 69 (2013)





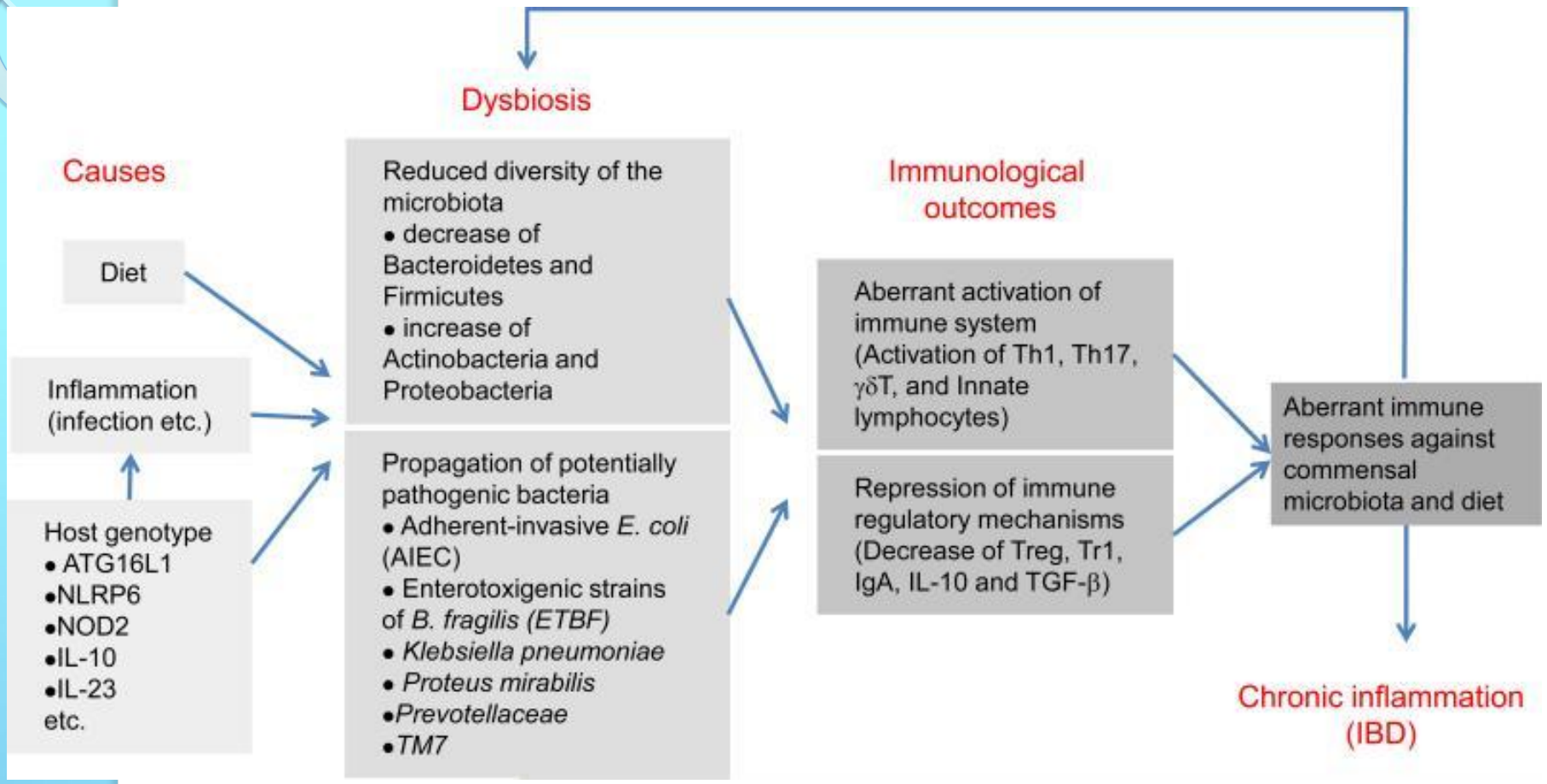


Thetaiotamicron Bacteroides

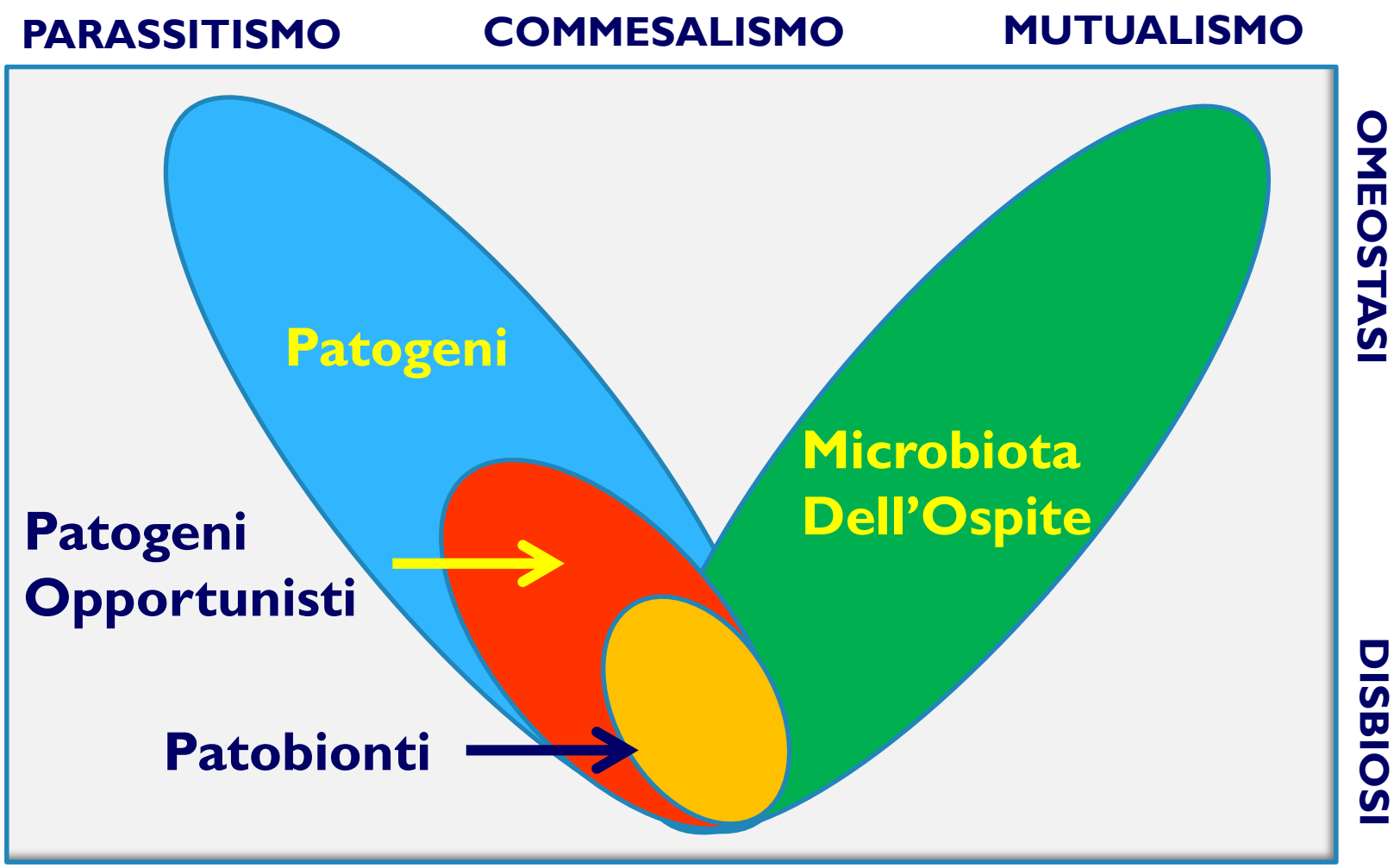
Metanobrevibacter Smithii

Fecalibacterium Prausnitzii

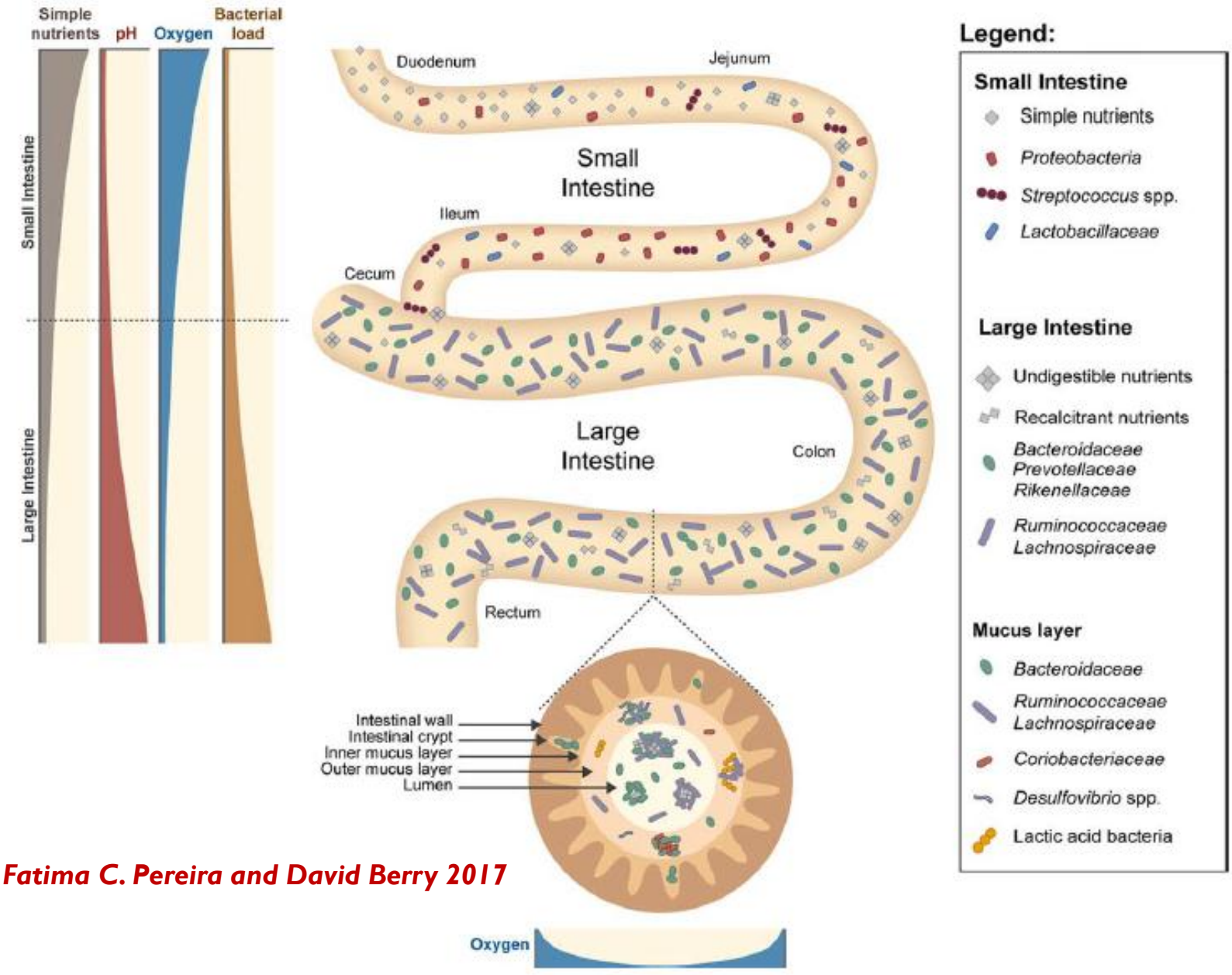
F Armougom et al. PLoS ONE 2009


Dysbiosis
Causes
Diet
Inflammation (infection etc.)
Host genotype
• ATG16L1
•NLRP6
•NOD2
•IL-10
•IL-23
etc.
Reduced diversity of the microbiota
• decrease of Bacteroidetes and Firmicutes
• increase of Actinobacteria and Proteobacteria
Propagation of potentially pathogenic bacteria
• Adherent-invasive E. coli (AIEC)
• Enterotoxigenic strains of B. fragilis (ETBF)
• Klebsiella pneumoniae
• Proteus mirabilis
•Prevotellaceae
•TM7
Immunological outcomes
Aberrant activation of immune system (Activation of Th1, Th17, γδT, and Innate lymphocytes)
Repression of immune regulatory mechanisms (Decrease of Treg, Tr1, IgA, IL-10 and TGF-β)
Aberrant immune responses against commensal microbiota and diet
Chronic inflammation (IBD)

Dall'Eubiosi alla Disbiosi



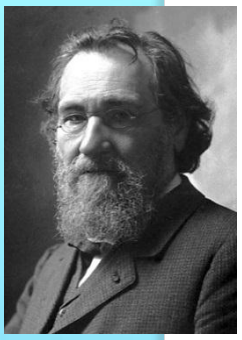
Stecher B et al. Nat. Rev Microbiol 2013



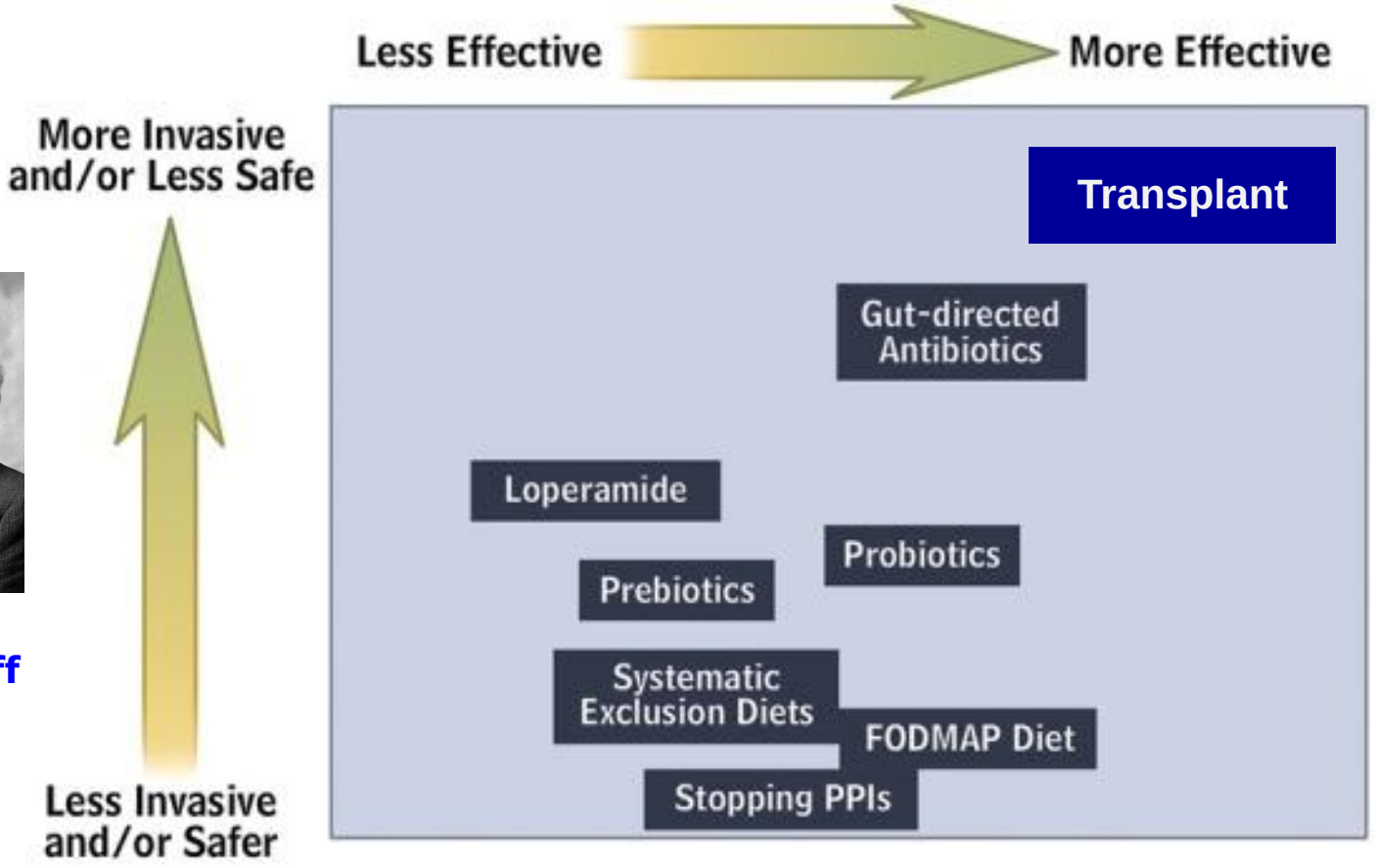
Fatima C. Pereira and David Berry 2017

Come modificare il microbiota

Come modificare il microbiota



Ilya Ilich Metchnikoff



Magnus Simre, Giovanni Barbara et al. - Gut 2013;62:159–176 (modificato)


The Future
NEXT EXIT

Take Home messages

- ☑ Interazione fra microorganismi ed ospite
- ☑ Metaboloma
- ☑ Il digiuno modifica il microbioma
- ☑ I nutrienti modificano il microbioma

GRAZIE

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