Microbiota intestinale…
l'organo fragile

Vito Leonardo Miniello

Nutrition Unit

UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

Napule è…

PEDIATRIA PREVENTIVA E SOCIALE

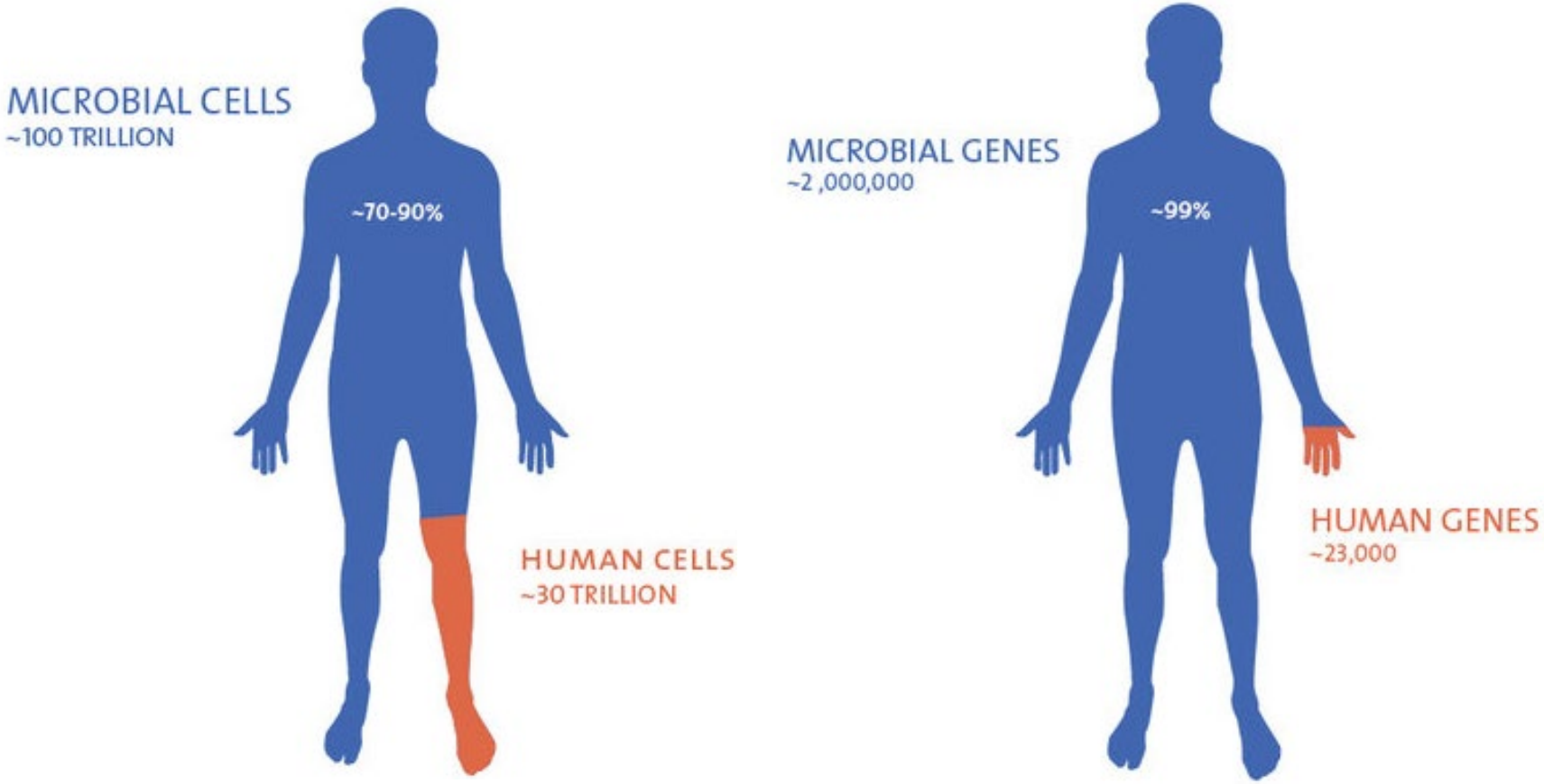
Società Italiana di Pediatria SIPPS

Homo bacteriens and a network of surprises

B. HENDERSON and M. WILSON[1]

100 % Human?

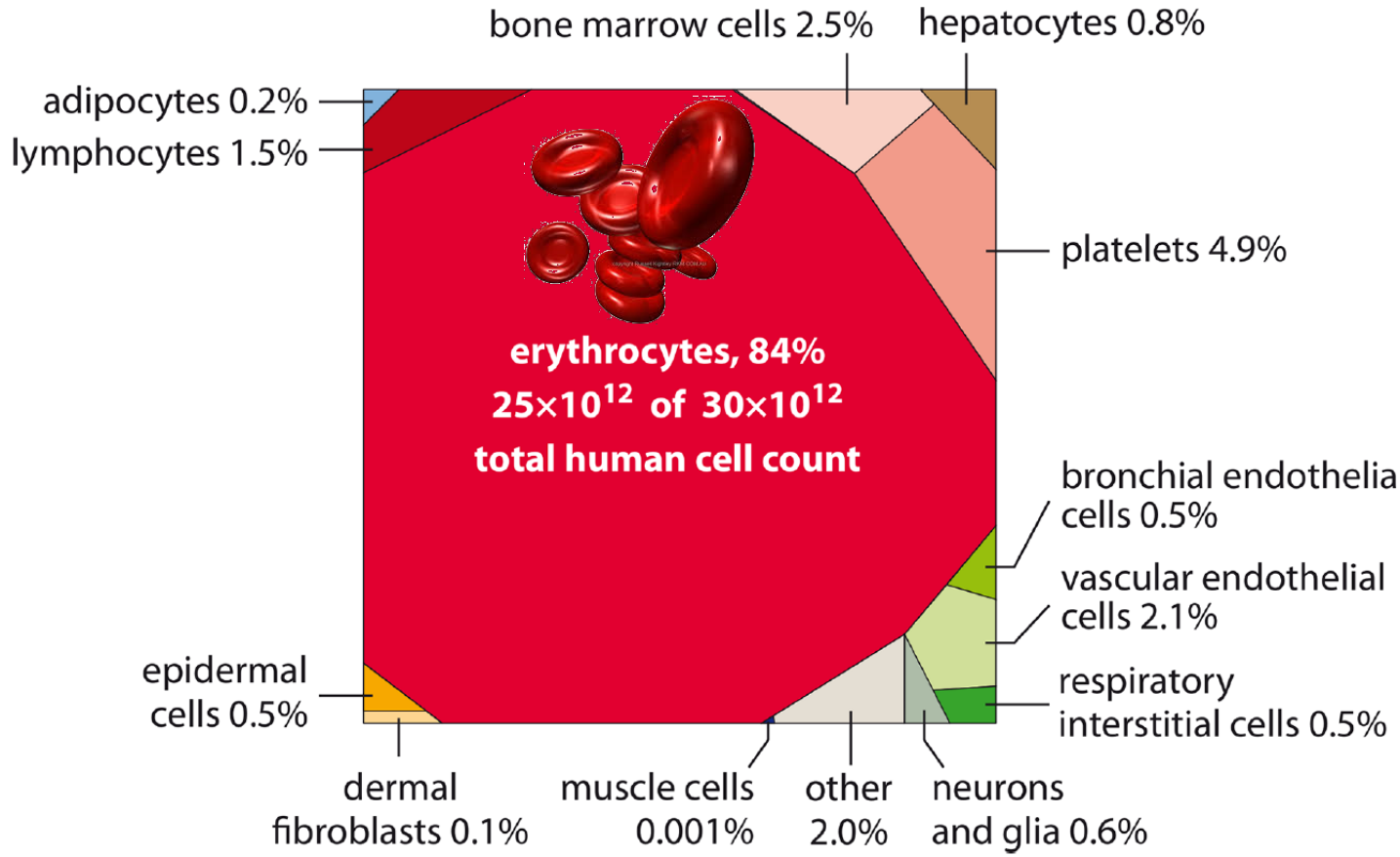
100 % Human?


MICROBIAL CELLS
~100 TRILLION
~70-90%
HUMAN CELLS
~30 TRILLION
MICROBIAL GENES
~2 ,000,000
~99%
HUMAN GENES
~23,000

Revised Estimates for the Number of Human and Bacteria Cells in the Body

Ron Sender[1], Shai Fuchs[2¤]*, Ron Milo[1]*

PLOS Biology 2016

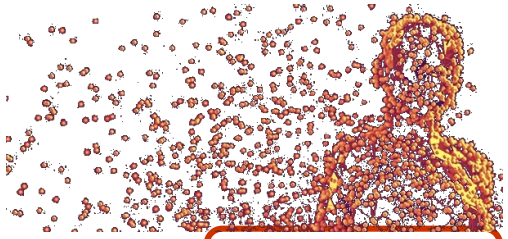


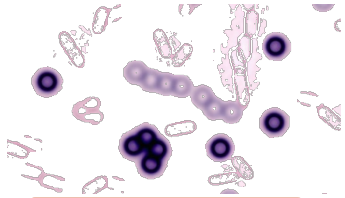
The distribution of the number of human cells by cell type.

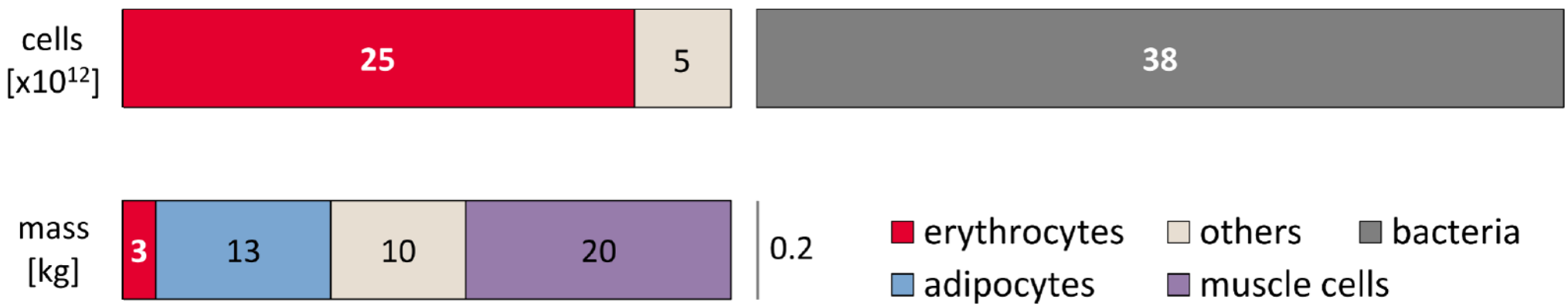
Revised Estimates for the Number of Human and Bacteria Cells in the Body

Ron Sender[1], Shai Fuchs[2¤]*, Ron Milo[1]*

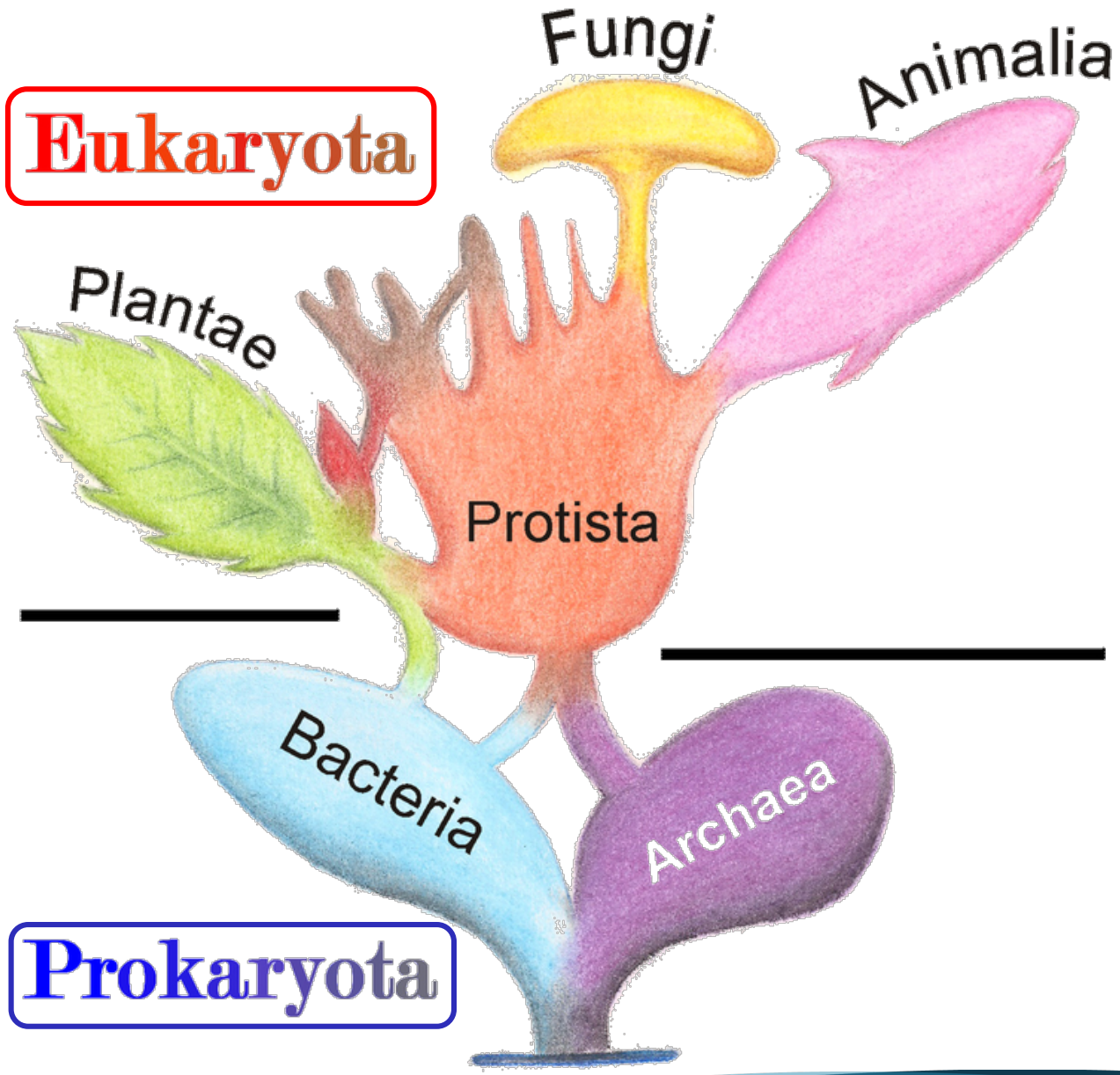
PLOS Biology 2016

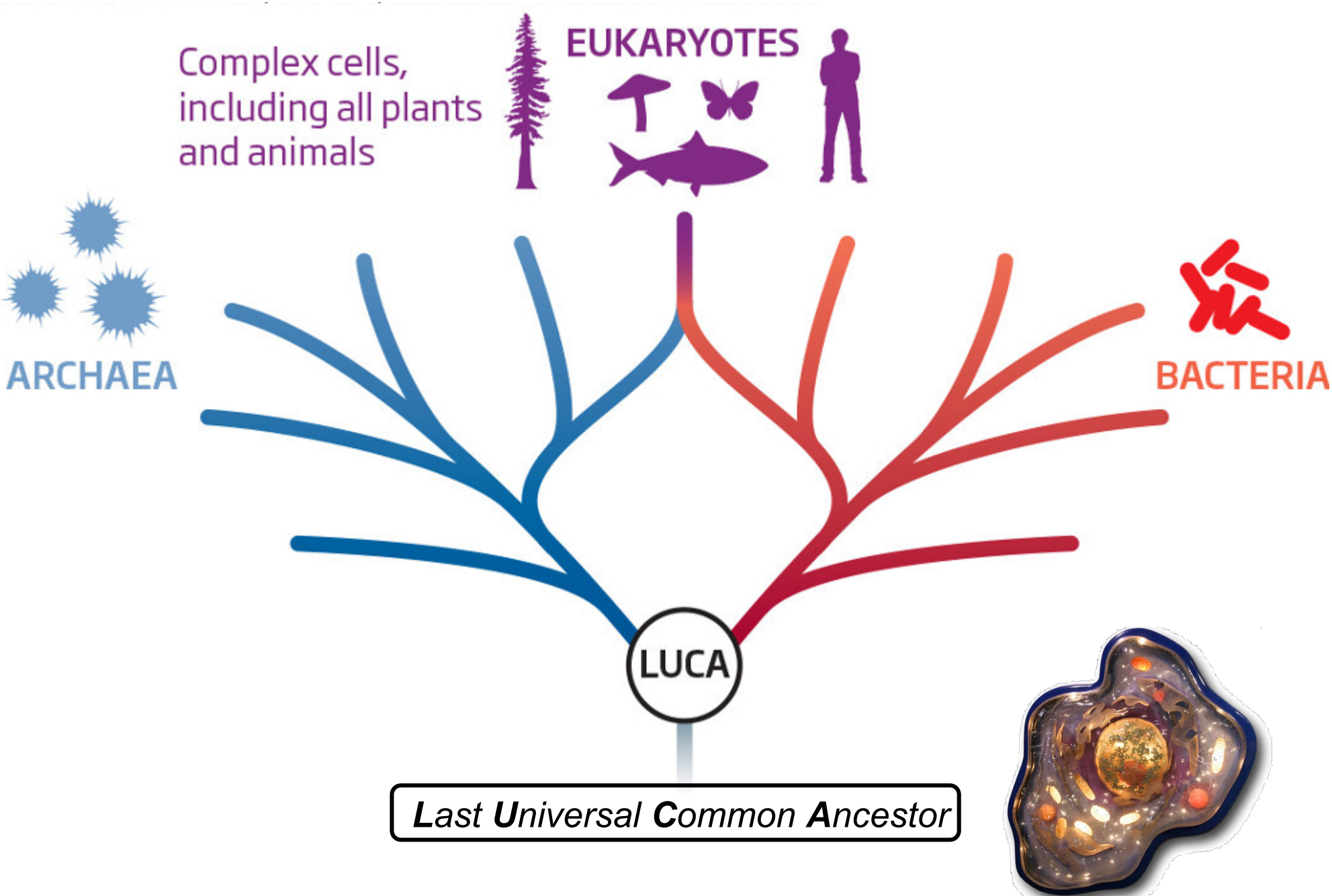




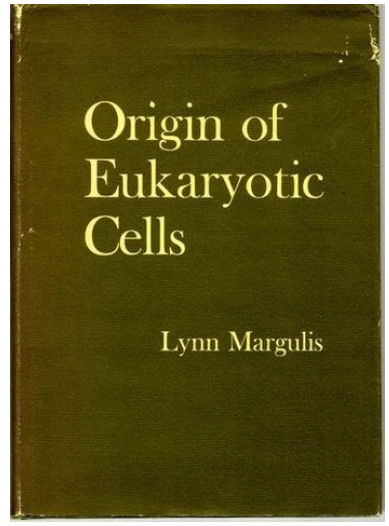


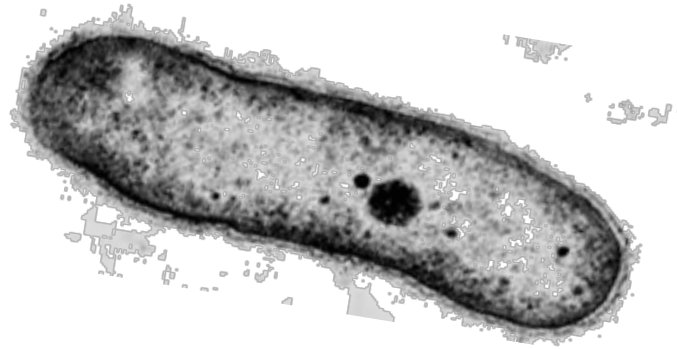
Distribution of cell number and mass for different cell types in the human body (for a 70 kg adult man)

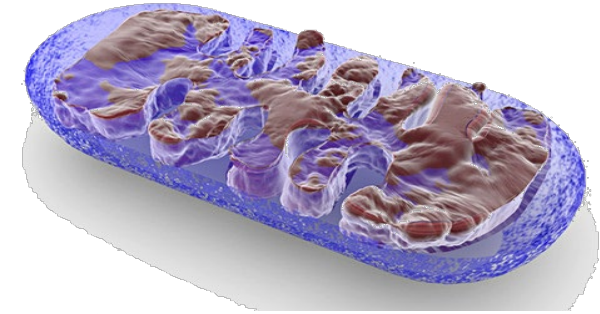

Eukaryota
Fungi
Animalia
Plantae
Protista
Bacteria
Archaea
Prokaryota

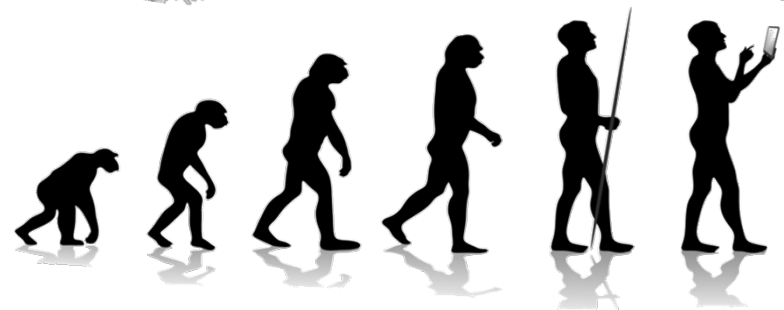

Complex cells,
including all plants
and animals
EUKARYOTES
ARCHAEA
BACTERIA
LUCA
Last Universal Common Ancestor

Endosymbiotic Theory



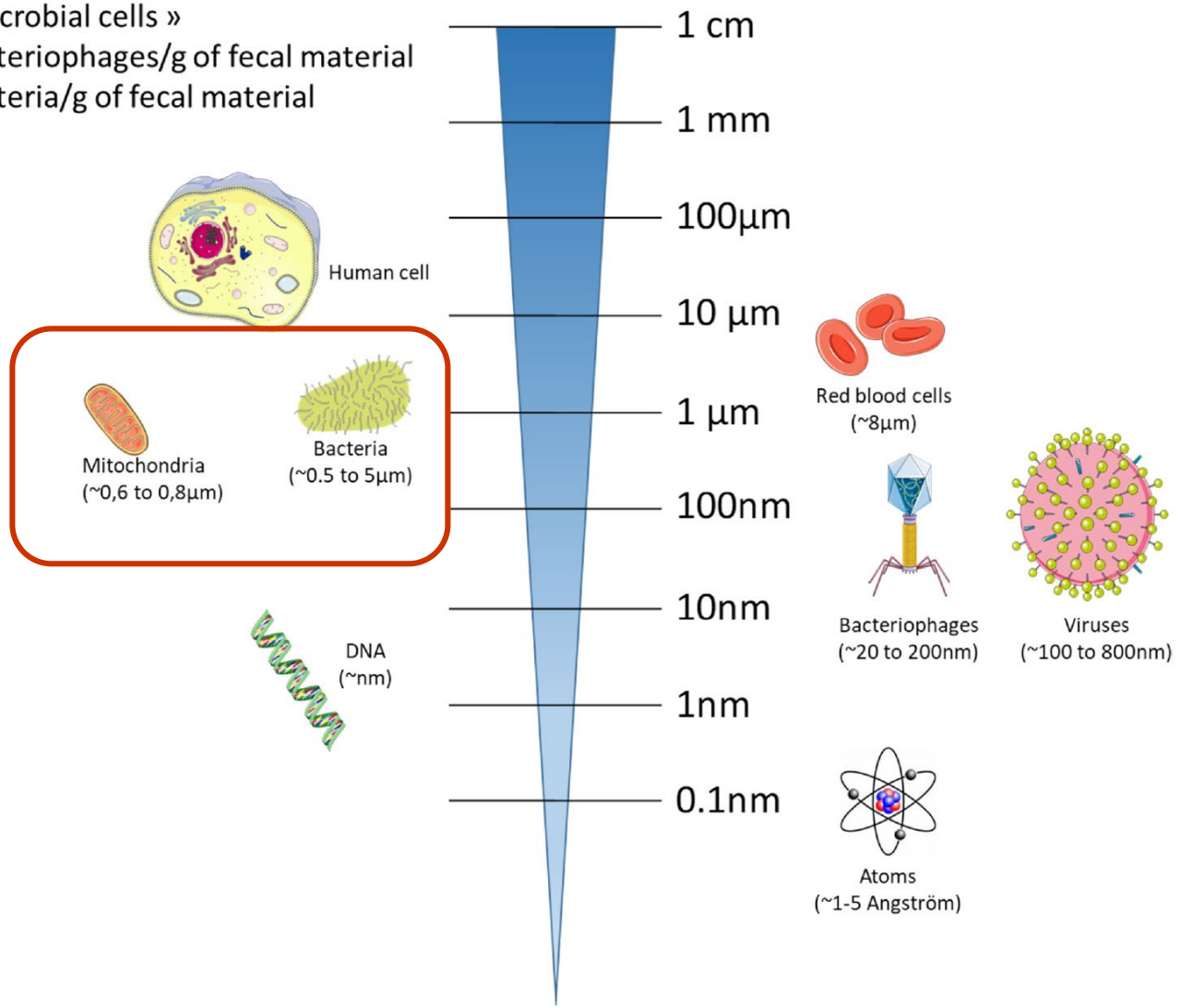




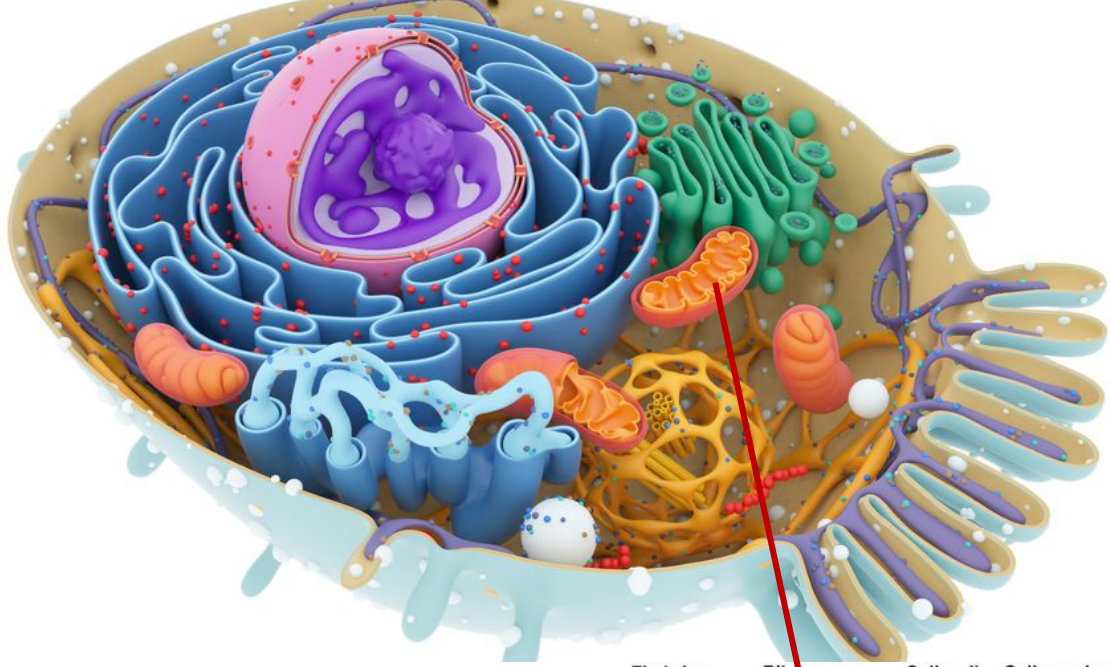


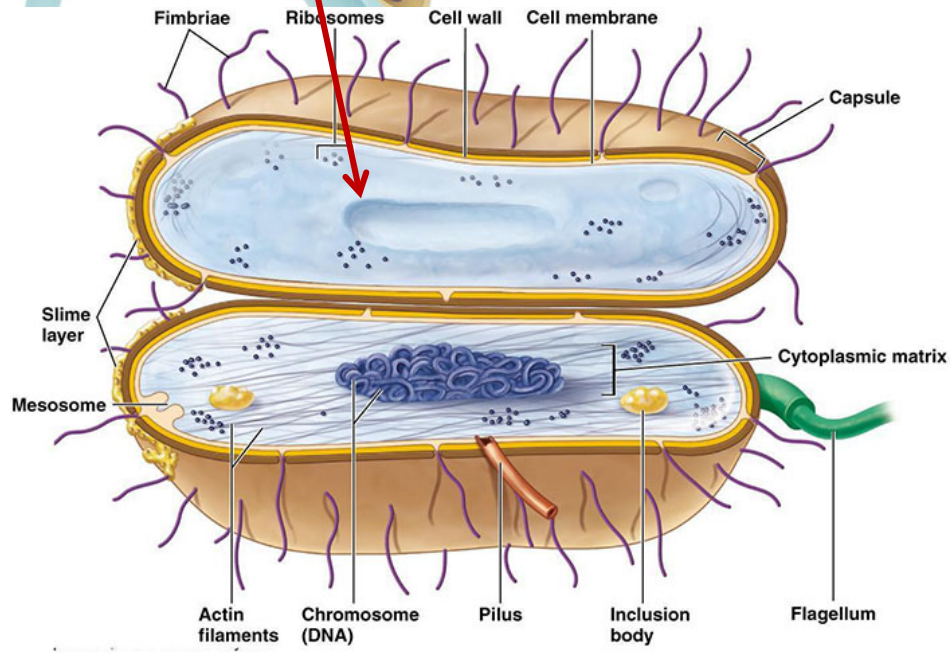
In the human body:

10^{13} « human cells »
10^{14} « microbial cells »
10^{12} bacteriophages/g of fecal material
10^{11} bacteria/g of fecal material

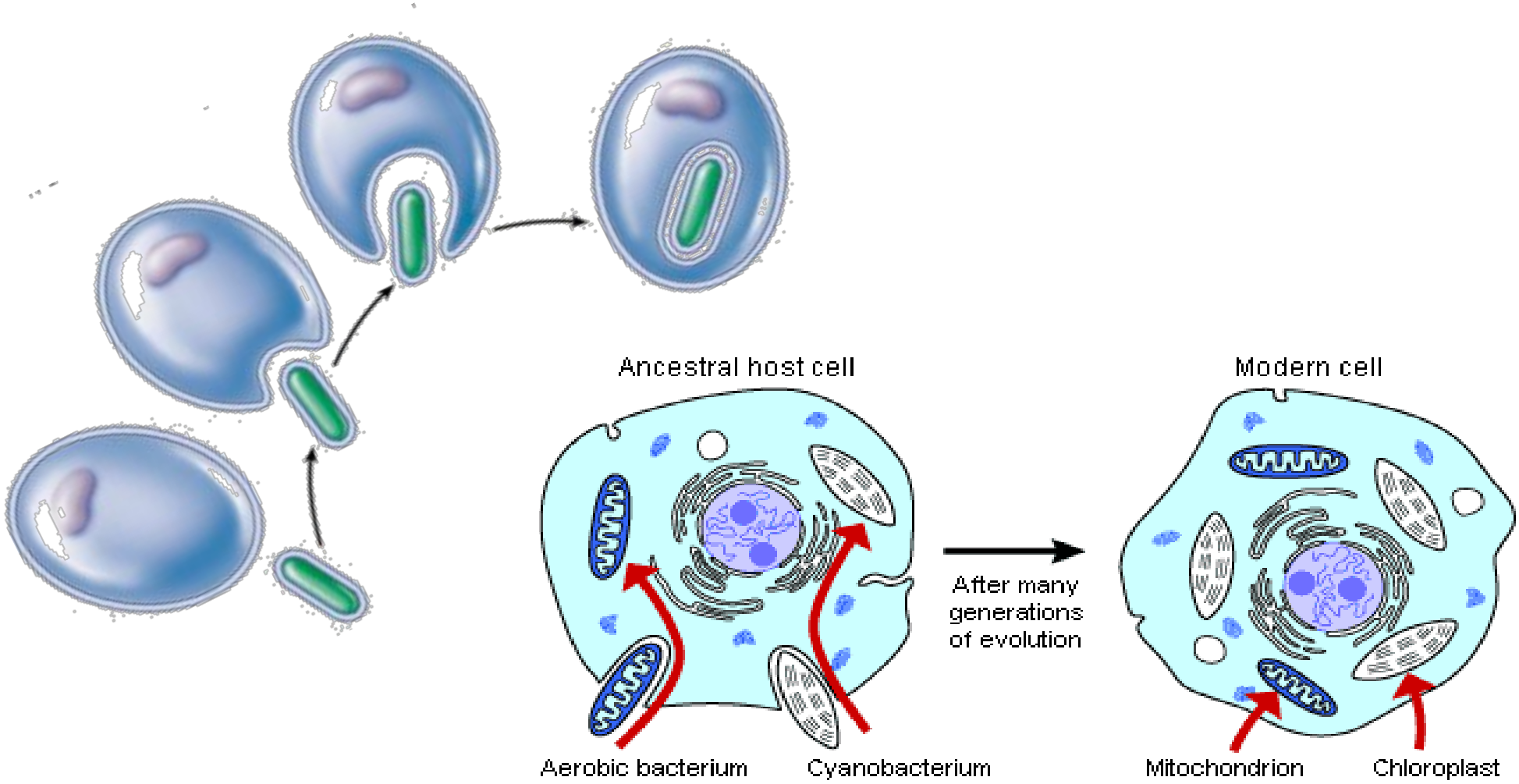


Cani PD. *Gut* 2018




Fimbriae
Ribosomes
Cell wall
Cell membrane
Capsule
Slime layer
Cytoplasmic matrix
Mesosome
Actin filaments
Chromosome (DNA)
Pilus
Inclusion body
Flagellum

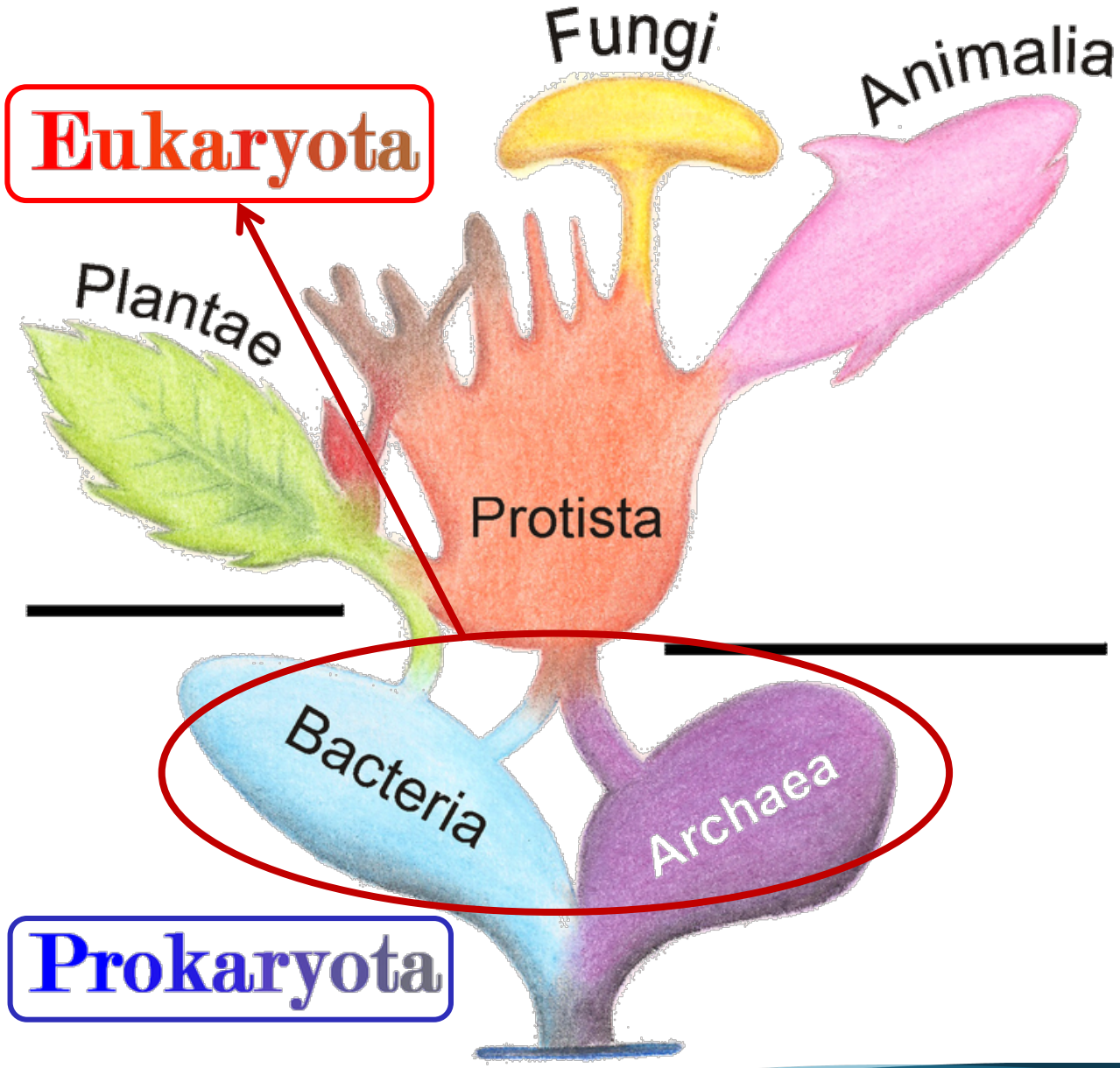
Endosymbiotic Theory



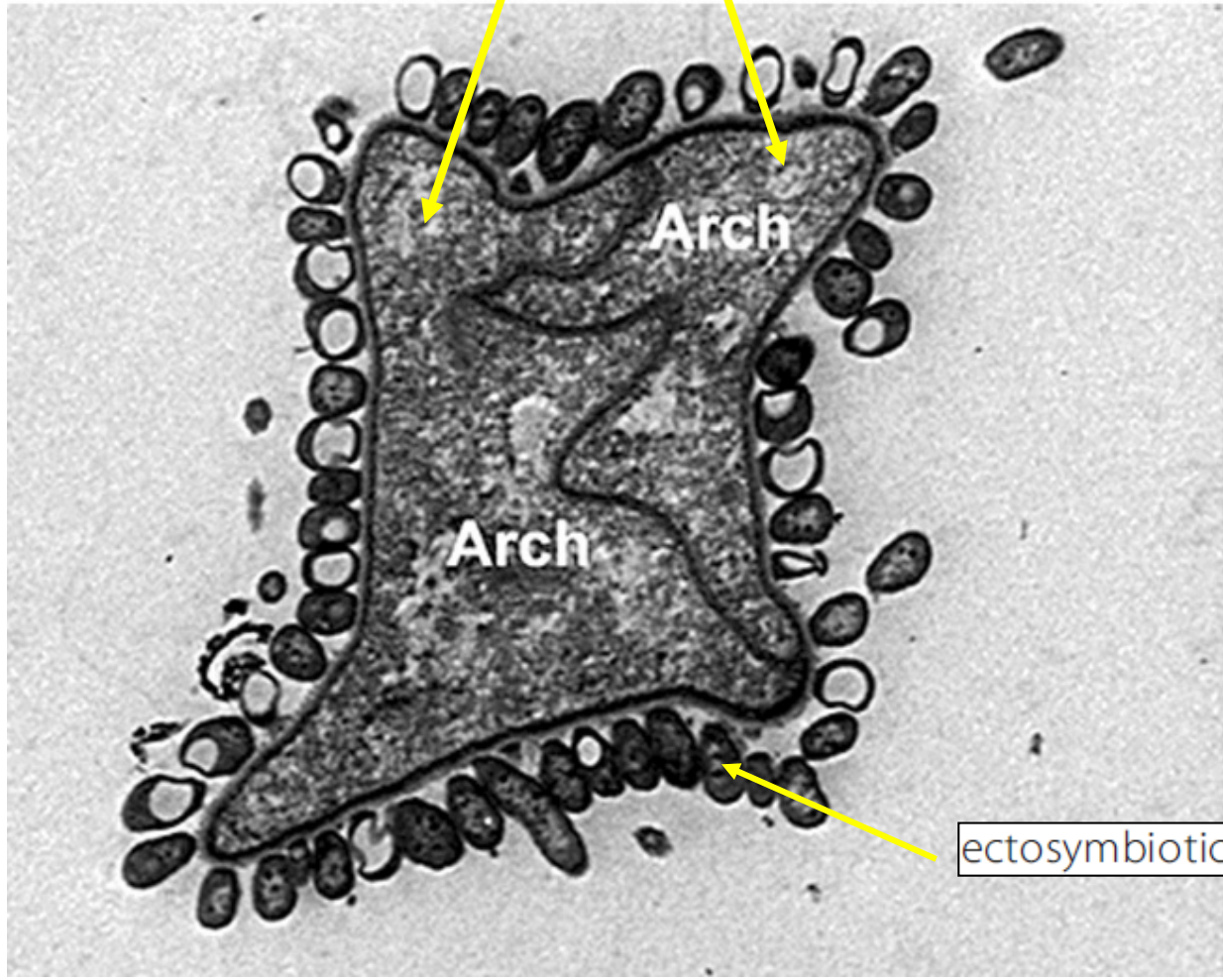
An inside-out origin for the eukaryotic cell

David A Baum

Buzz Baum

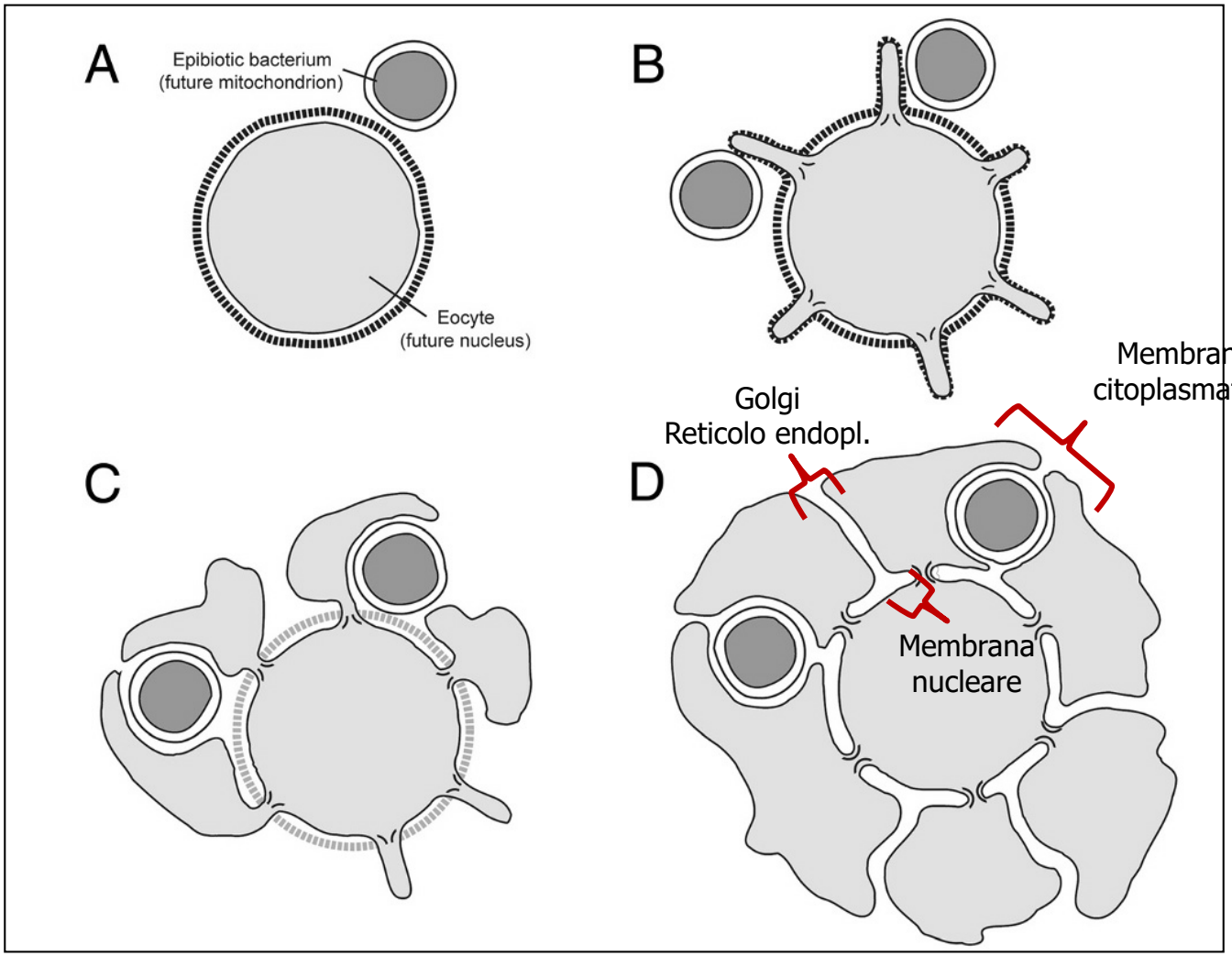

Fungi
Animalia
Eukaryota
Plantae
Protista
Bacteria
Archaea
Prokaryota

epibiotic bacteria associated with archaeal cells



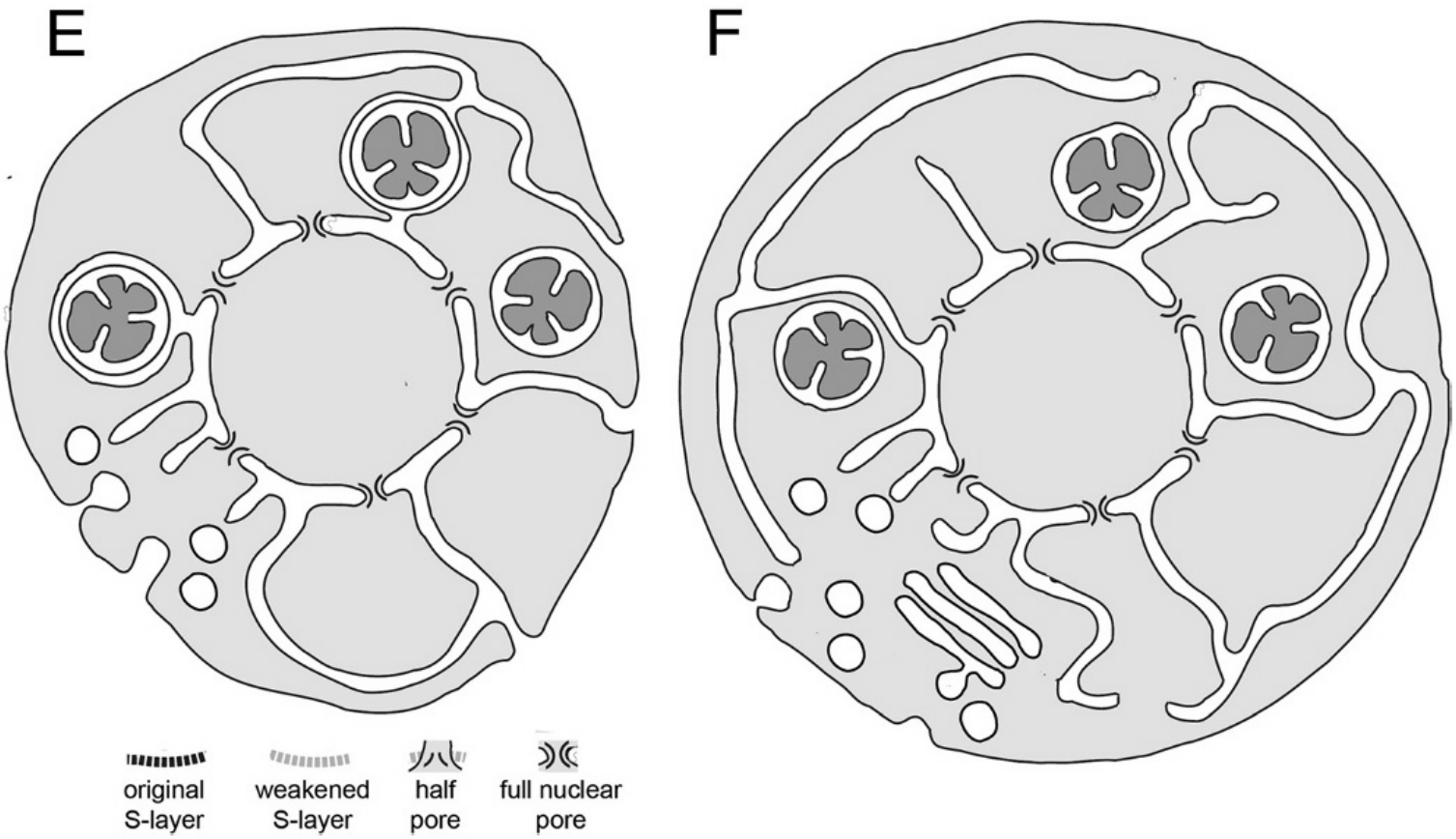
Muller F, Brissac T, Le Bris N, Felbeck H, Gros O: **First description of giant Archaea (Thaumarchaeota) associated with putative bacterial ectosymbionts in a sulfidic marine habitat.** *Environ Microbiol* 2010, **12**:2371–2383.

An inside-out origin for the eukaryotic cell



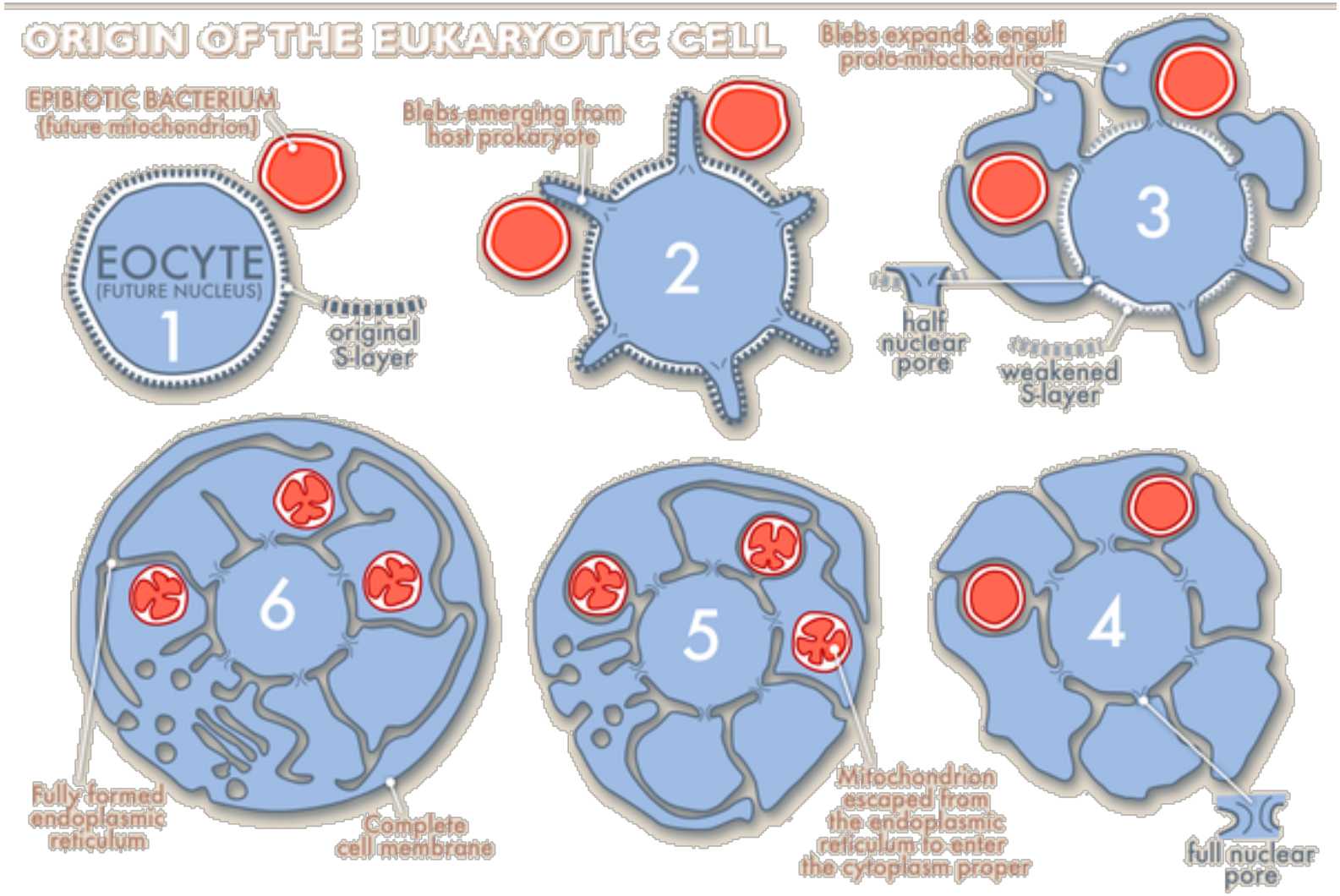
Baum and Baum *BMC Biology* 2014

An inside-out origin for the eukaryotic cell



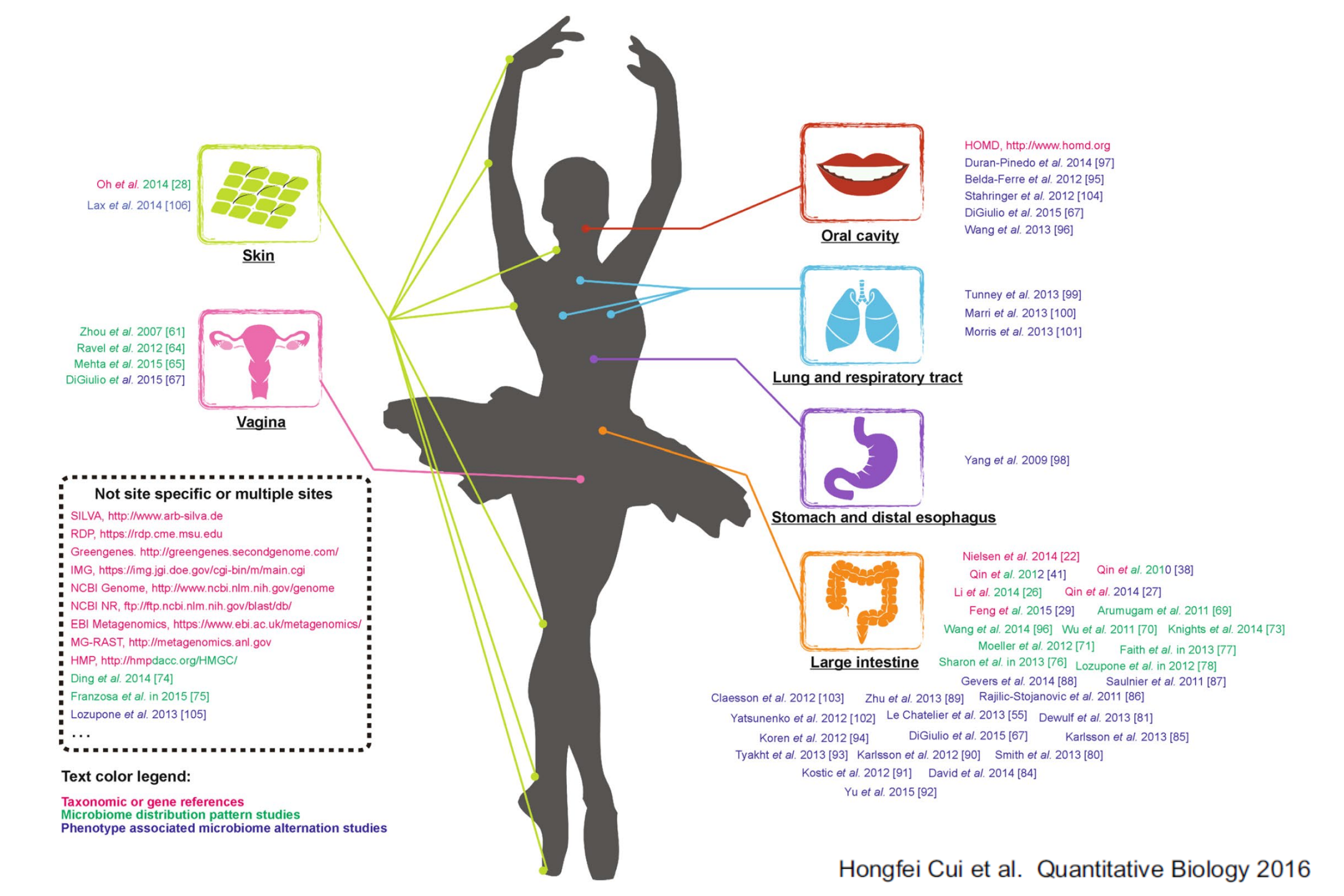
Baum and Baum *BMC Biology* 2014

An inside-out origin for the eukaryotic cell



Baum and Baum *BMC Biology* 2014

AUGUST 18TH - 24TH 2012 Worldwide cover

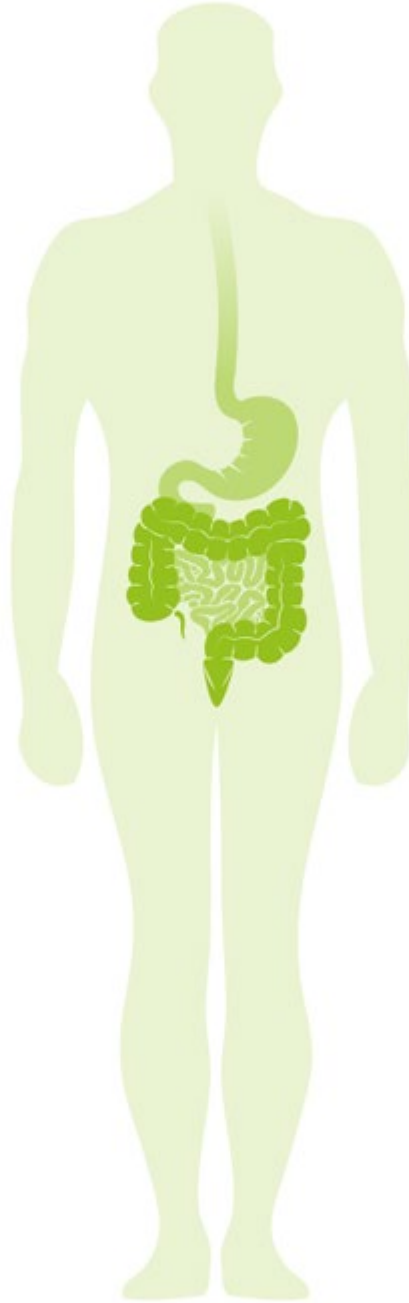


Hongfei Cui et al. Quantitative Biology 2016

MAKE
vitamins, including
B12, K AND FOLATE

TEACH
THE IMMUNE SYSTEM
to tell friends from foes

PRODUCE
IMPORTANT MOLECULES
that travel around the body

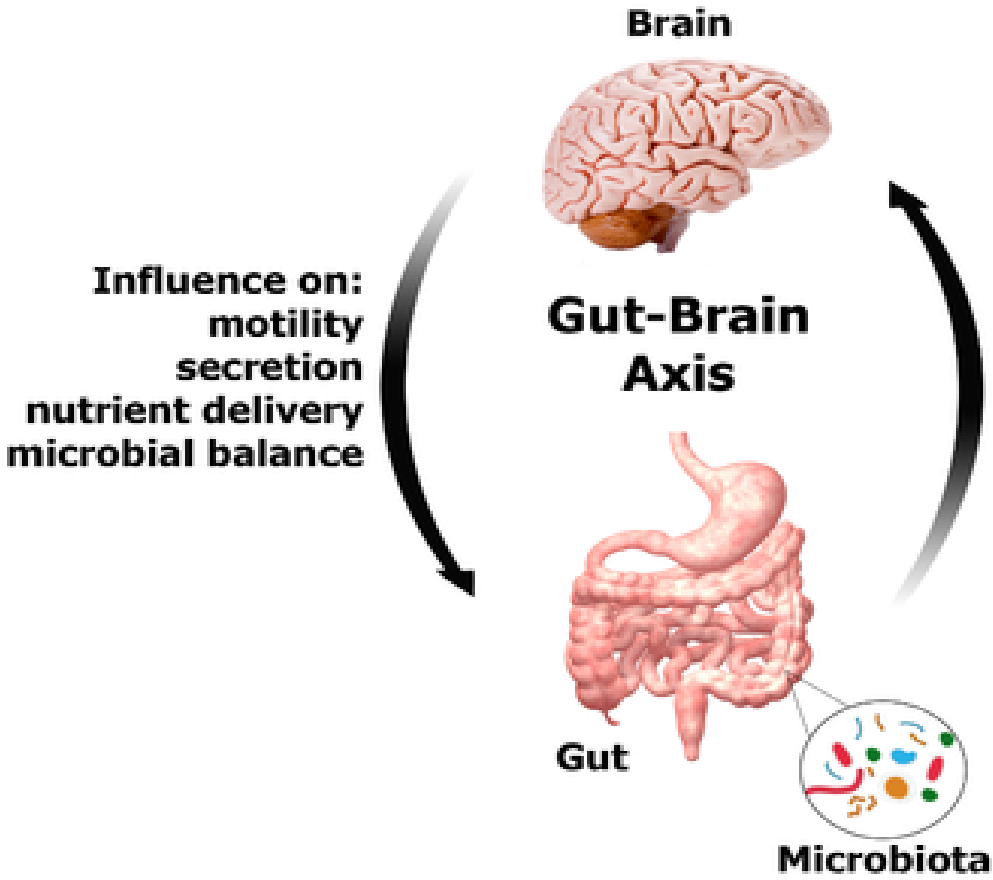


DEFEND
against harmful
MICROORGANISMS

INFLUENCE
the calories you harvest

HELP
PRODUCE SEROTONIN,
important for optimal
GUT FUNCTION

Asse microbiota-intestino-cervello



Gut microbiota biomodulators, when the stork comes by the scalpel

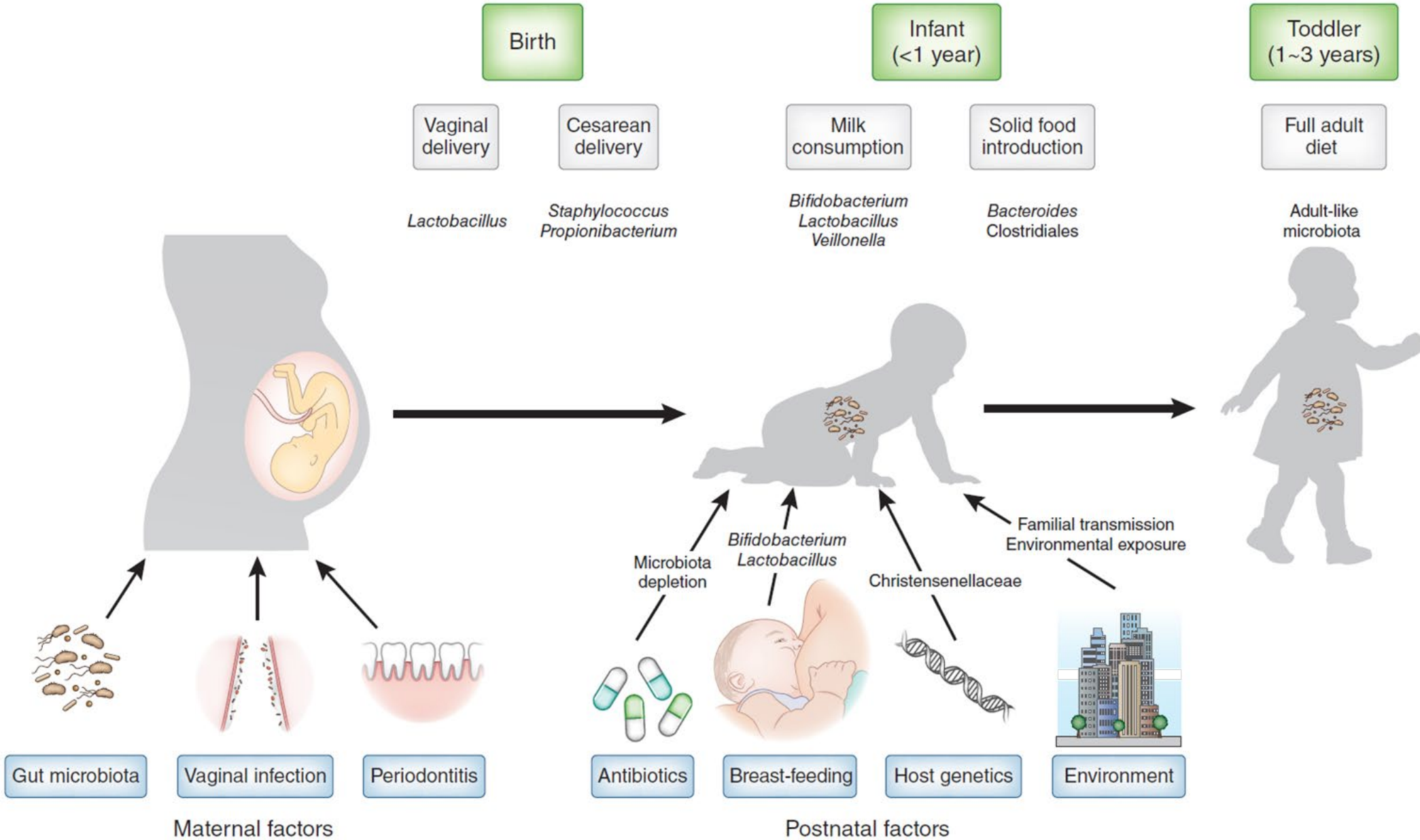
Vito Leonardo Miniello *, Angela Colasanto, Fernanda Cristofori, Lucia Diaferio, Laura Ficele, Valentina Santoiemma, Ruggiero Francavilla

Clinica Chimica Acta 451 (2015)

Journal of Probiotics & Health
ISSN: 2329-8901
2017, 5:1
Review Article

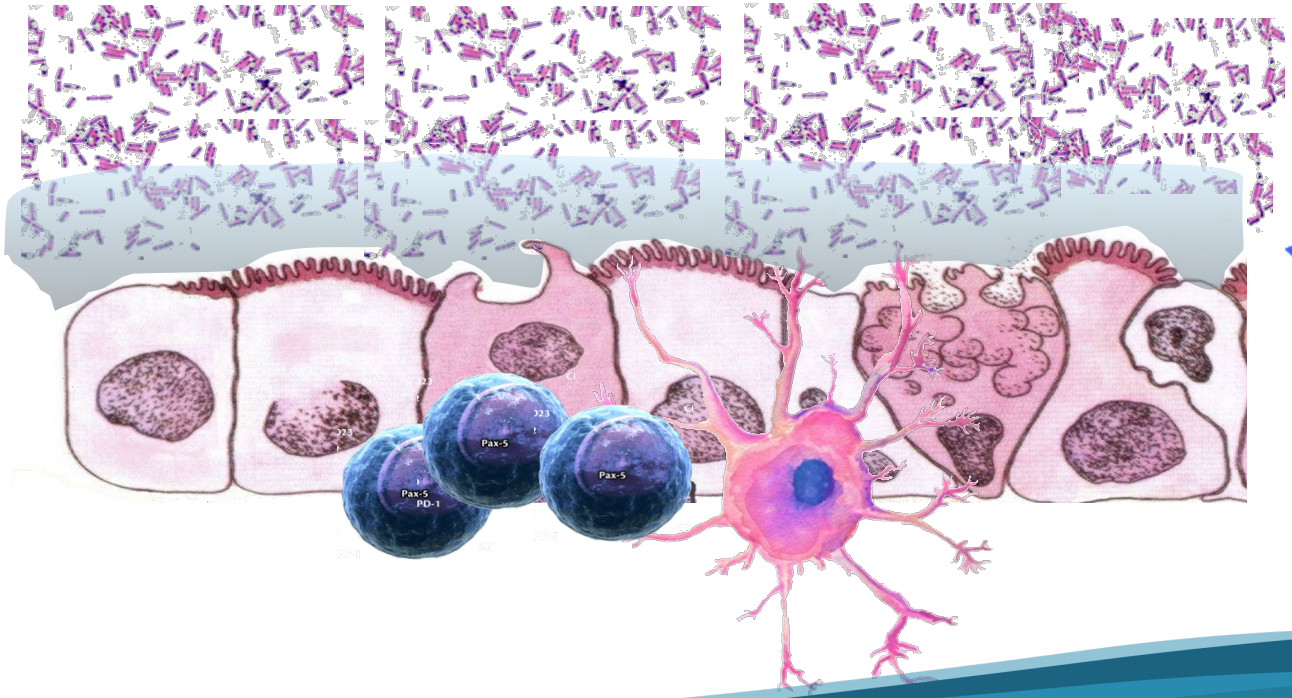
The Importance of Being Eubiotic

Vito Leonardo Miniello[1], Lucia Diaferio[1], Carlotta Lassandro[2] and Elvira Verduci[2*]

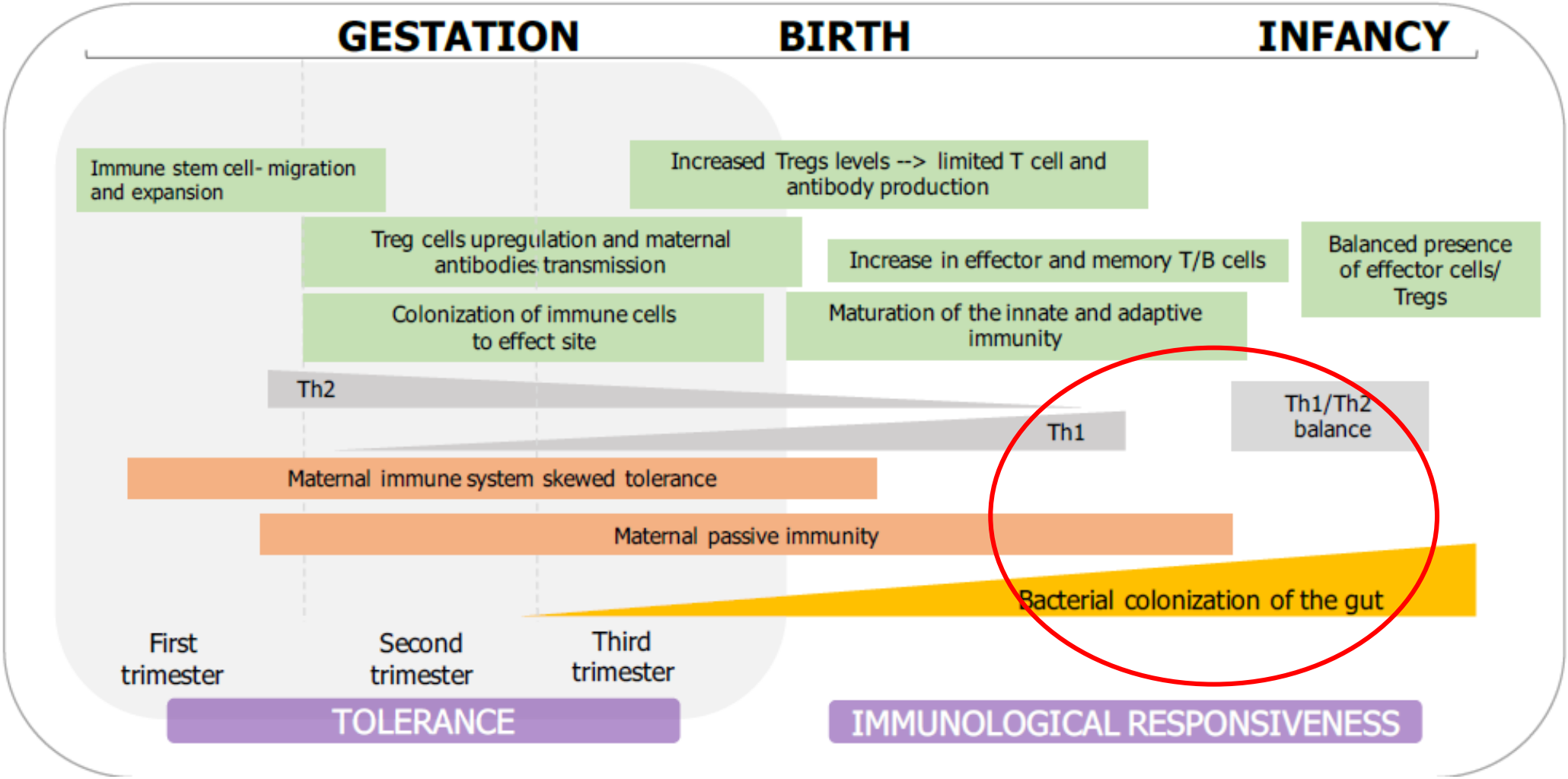


Sabrina Tamburini **NATURE MEDICINE** 2016

Il microbiota intestinale è un *organo batterico* **immuno-modulante**



Gut Microbiota and Mucosal Immunity in the Neonate

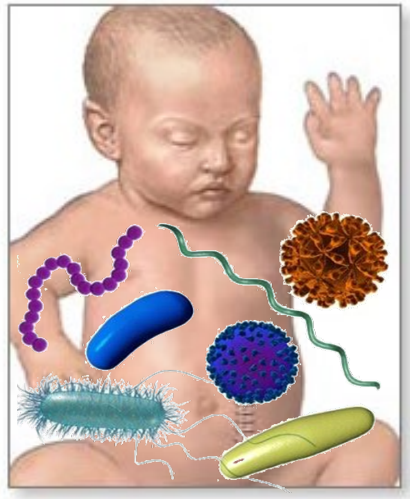


Majda Dzidic *Med. Sci.* 2018

Ipotesi Igiene

Th2

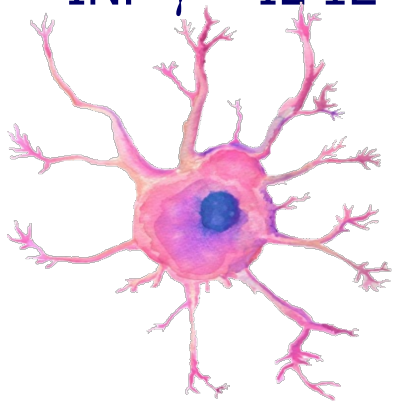
Th1



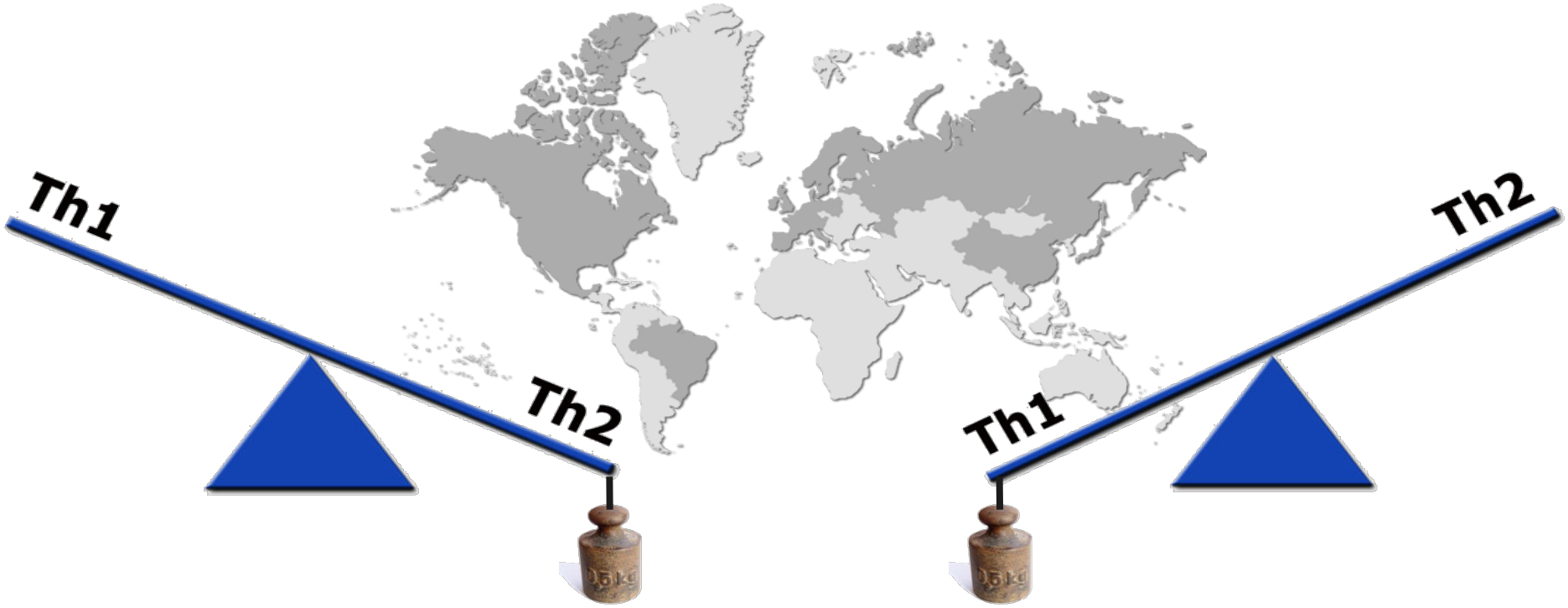
infections

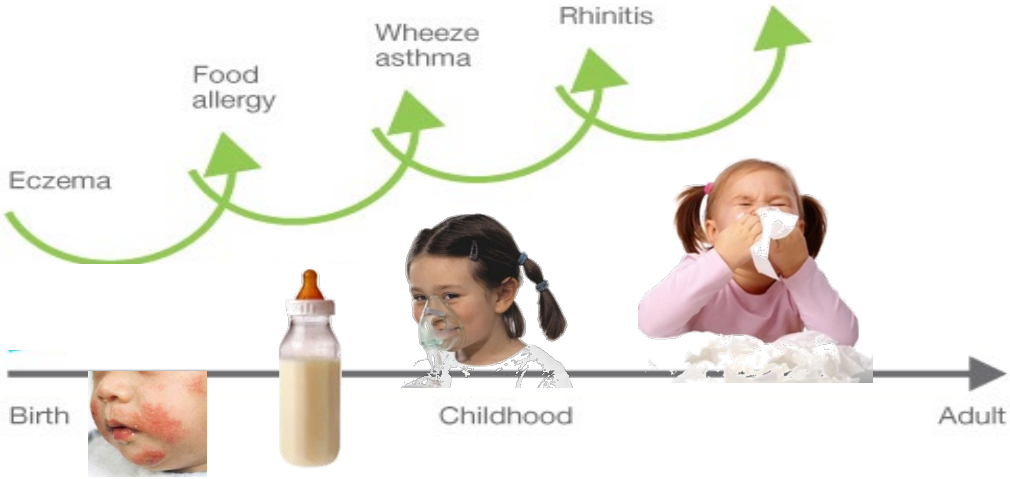
Strachan DP, 1989

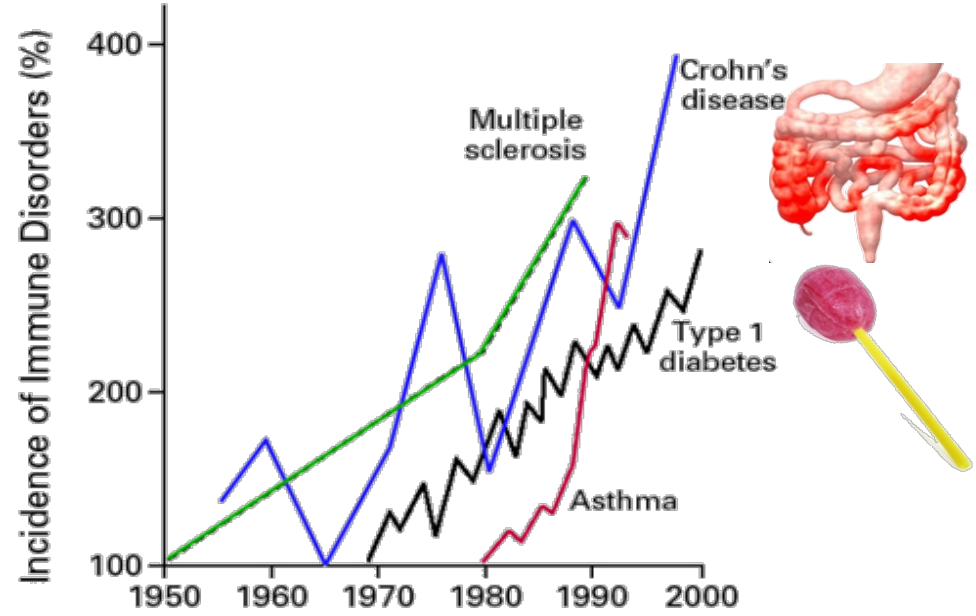
INF-γ IL-12



tolerogenic dendritic cells


Th1
Th2
Th2
Th1


Eczema
Food allergy
Wheeze asthma
Rhinitis
Birth
Childhood
Adult

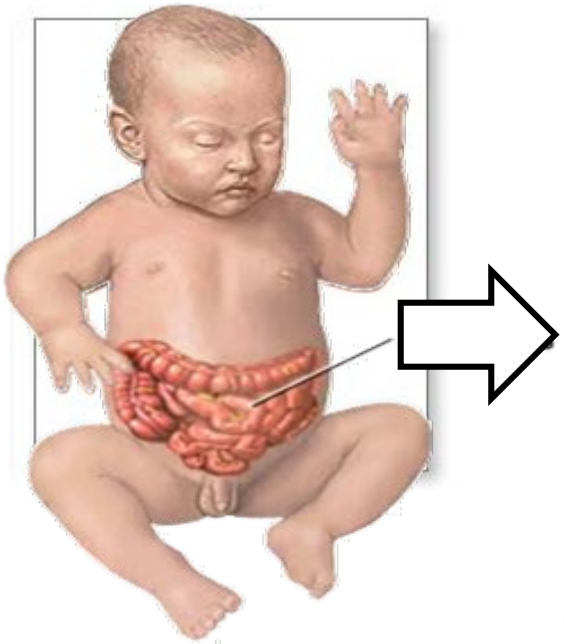

Incidence of Immune Disorders (%)
400
300
200
100
1950
1960
1970
1980
1990
2000
Multiple sclerosis
Crohn's disease
Type 1 diabetes
Asthma

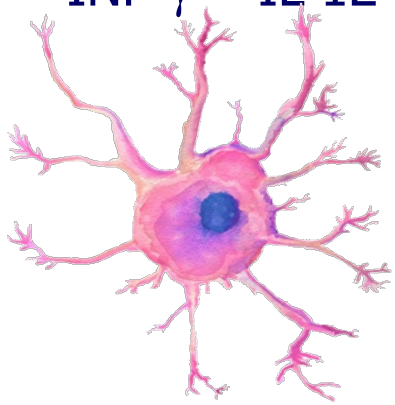
Ipotesi biodiversità microbica

Th2

Th1

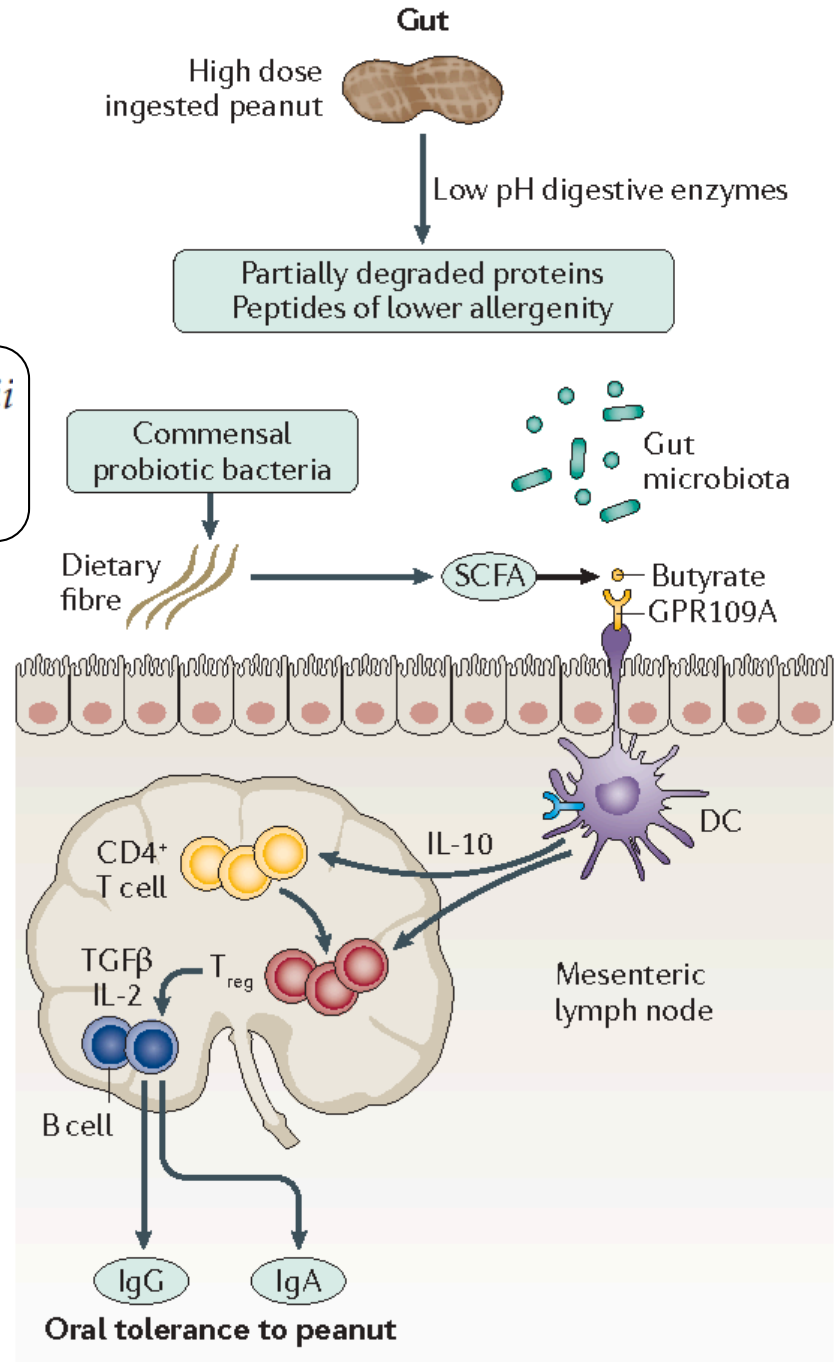
INF-γ IL-12





tolerogenic
dendritic cells

Faecalibacterium prausnitzii
Roseburia intestinalis
Eubacterium rectale



EXPERT CONSENSUS DOCUMENT

The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics

Glenn R. Gibson[1], Robert Hutkins[2], Mary Ellen Sanders[3], Susan L. Prescott[4], Raylene A. Reimer[5], Seppo J. Salminen[6], Karen Scott[7], Catherine Stanton[8], Kelly S. Swanson[9], Patrice D. Cani[10], Kristin Verbeke[11] and Gregor Reid[12]

NATURE REVIEWS | GASTROENTEROLOGY & HEPATOLOGY

Published online 14 Jun 2017

the new definition of prebiotics

‘a substrate that is selectively utilized by host microorganisms conferring a health benefit’

It clarifies that prebiotic targets extend beyond stimulation of bifidobacteria and lactobacilli, and recognizes that health benefits can derive from effects on other beneficial taxa including (but not limited to) *Roseburia*, *Eubacterium* or *Faecalibacterium* spp.

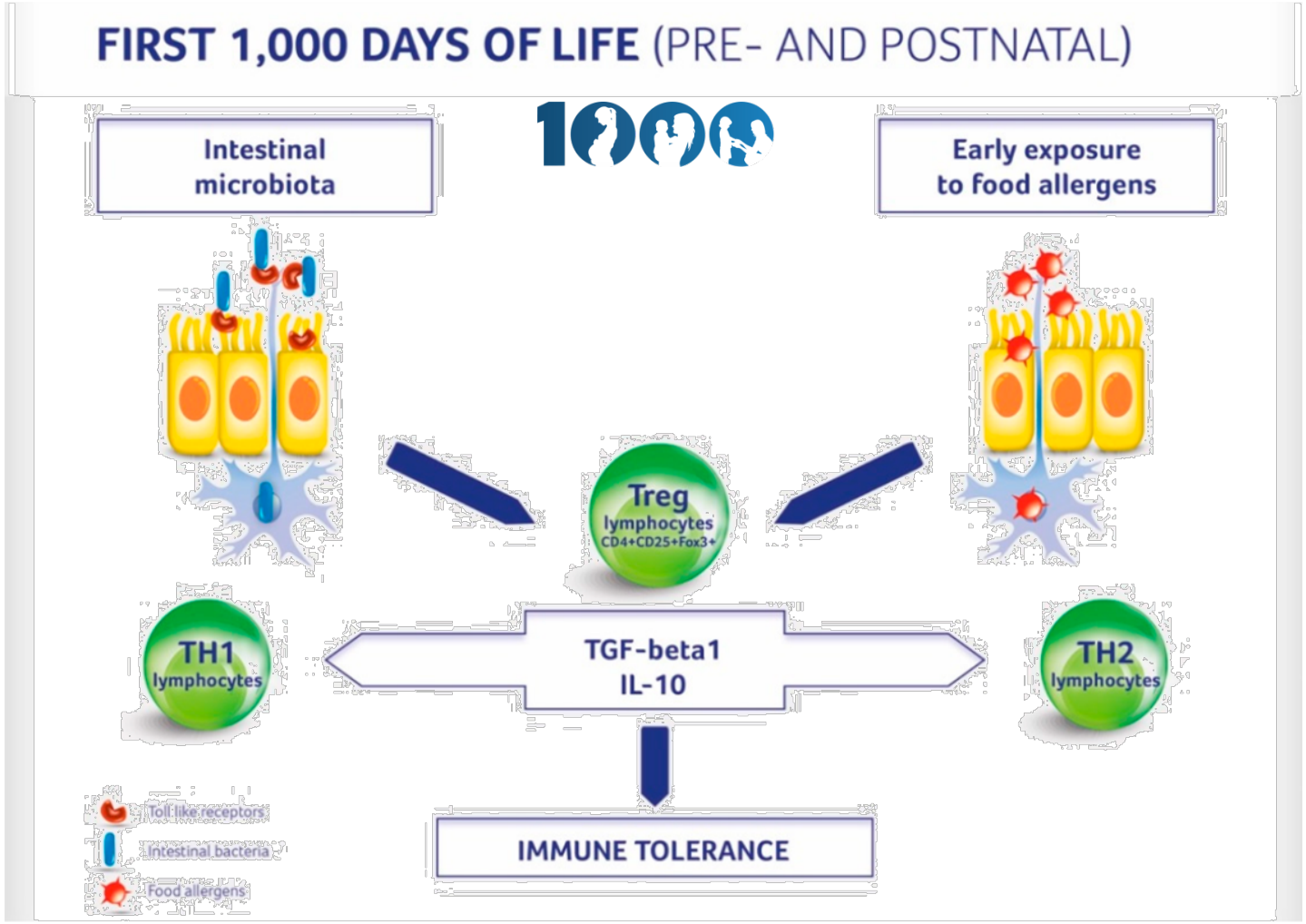
Food allergy: Update on prevention and tolerance

J Allergy Clin Immunol 2018

George Du Toit, MB, BCh,[a] Hugh A. Sampson, MD,[b] Marshall Plaut, MD,[c] A. Wesley Burks, MD,[d]

- **Ipotesi della biodiversità microbica intestinale**
- **Ipotesi della doppia barriera**
- **Ipotesi vitamina D**

Microbial and Nutritional Programming—The Importance of the Microbiome and Early Exposure to Potential Food Allergens in the Development of Allergies

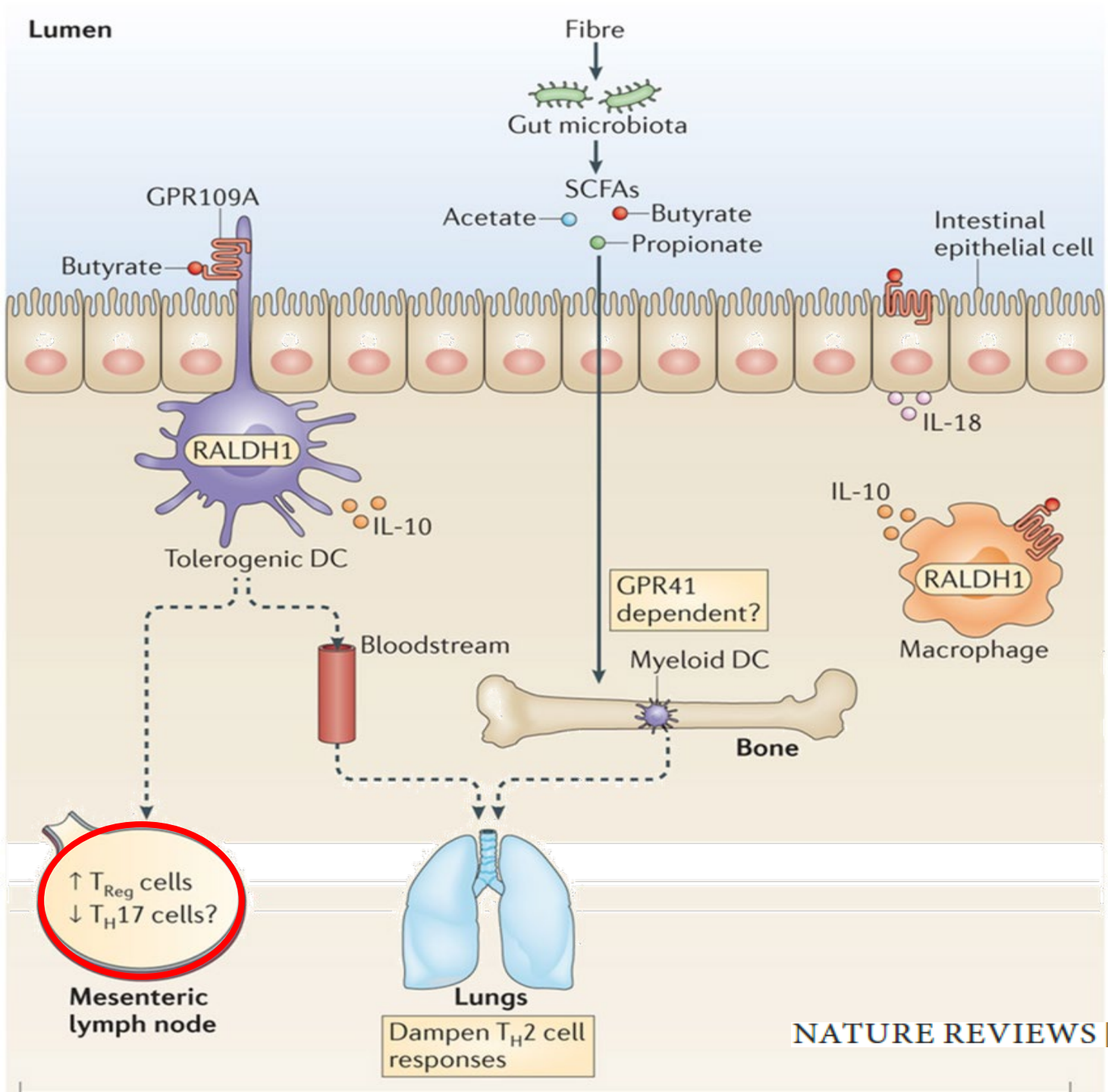


E tutti quei momenti andranno perduti nel tempo,
come lacrime nella pioggia

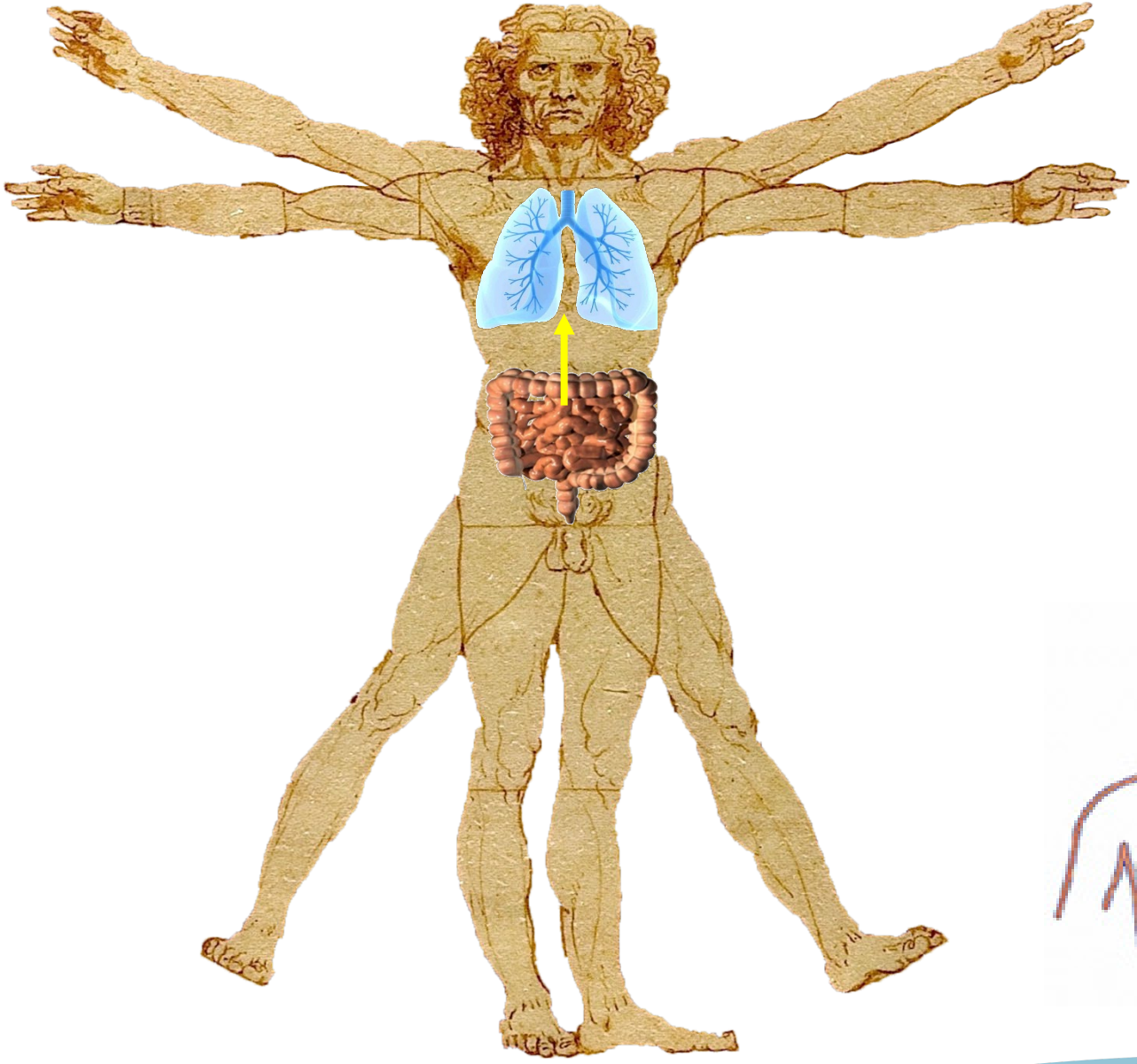
Early Development of the Gut Microbiome and Immune-Mediated Childhood Disorders

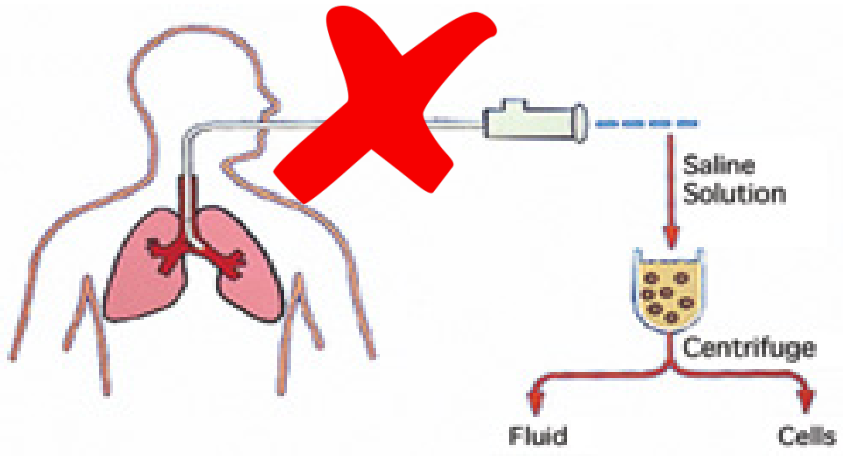
Min Li, PhD[1] Mei Wang, PhD[1] Sharon M. Donovan, PhD, RD[1] Semin Reprod Med 2014

GUT MICROBIOTA	ENVIRONMENTAL FACTORS	IMMUNE-MEDIATED DISORDERS
Cesarean delivered infants was initially colonized by bacteria from human skin; the early microbiota was less diverse, had lower number of beneficial bacteria, e.g. *Bifidobacterium* and *Bacteroides fragilis* group and more often colonized with *Clostridium difficile*.	**Delivery mode (caesarean delivery)** 	Increase risk of asthma and food allergy; had no effect on eczema Increase risk of IBD or no effect
Delayed colonization and reduced diversity; Increase potential pathogens, e.g. *Escherichia coli*, *Streptococcus*, *Enterococcus*, *Staphylococcus*, *Klebsiella* and *Clostridium* species; Decrease beneficial bacteria, e.g. *Bifidobacterium* and *Lactobacillus*.	**Gestation time (preterm)** 	Increase risk of NEC
In general, breastfed infants are colonized mainly by *Bifidobacterium*, while formula-fed infants harbor a more diverse microbiota, including *Bacteroides*, clostridia, *Enterococcus* and *Enterobacteriaceae* in addition to *Bifidobacterium*.	**Feeding type (breastfeeding)** 	Decrease risk of asthma and food allergy; except when mothers have atopic diseases. For eczema, results are controversy: breastfeeding decreases, has no effect or increases eczema. Protective effect on IBD
Altered microbial colonization; Antibiotic treated infants had less diversity with attenuation of the colonization of some beneficial bacteria, such as *Bifidobacterium* and overgrowth of potential pathogens, e.g. *Enterobacteriaceae*.	**Antibiotic exposure** 	Increase risk of asthma, eczema, food allergy, NEC, IBD, IBS
Prebiotics increase beneficial bacteria counts: e.g. *Bifidobacterium* and *Lactobacillus*. Probiotics increase beneficial bacteria: e.g. *Lactobacillus*; decrease potential pathogens, e.g. *Enterobacteriaceae*.	**Pre/probiotic use** 	Prebiotics decrease eczema and asthma in infants at high risk of allergy. Combined pre- and postnatal probiotic treatment reduce risk of eczema; Probiotics lower incidence of NEC. Probiotics induce remission maintenance of ulcerative colitis



NATURE REVIEWS | IMMUNOLOGY
2015




Saline
Solution
Centrifuge
Fluid
Cells

Lactobacillus reuteri Modulates Cytokines Production in Exhaled Breath Condensate of Children With Atopic Dermatitis

Vito Leonardo Miniello, Luigia Brunetti, Riccardina Tesse, Miria Natile, Lucio Armenio, and Ruggiero Francavilla

JPGN • Volume 50, Number 5, May 2010

Eczema ATOPICO

Eczema NON atopico

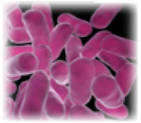
SCORAD

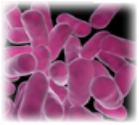
IFN-γ IL-4

(nell'esalato condensato)

SCORAD

SCORing Atopic Dermatitis





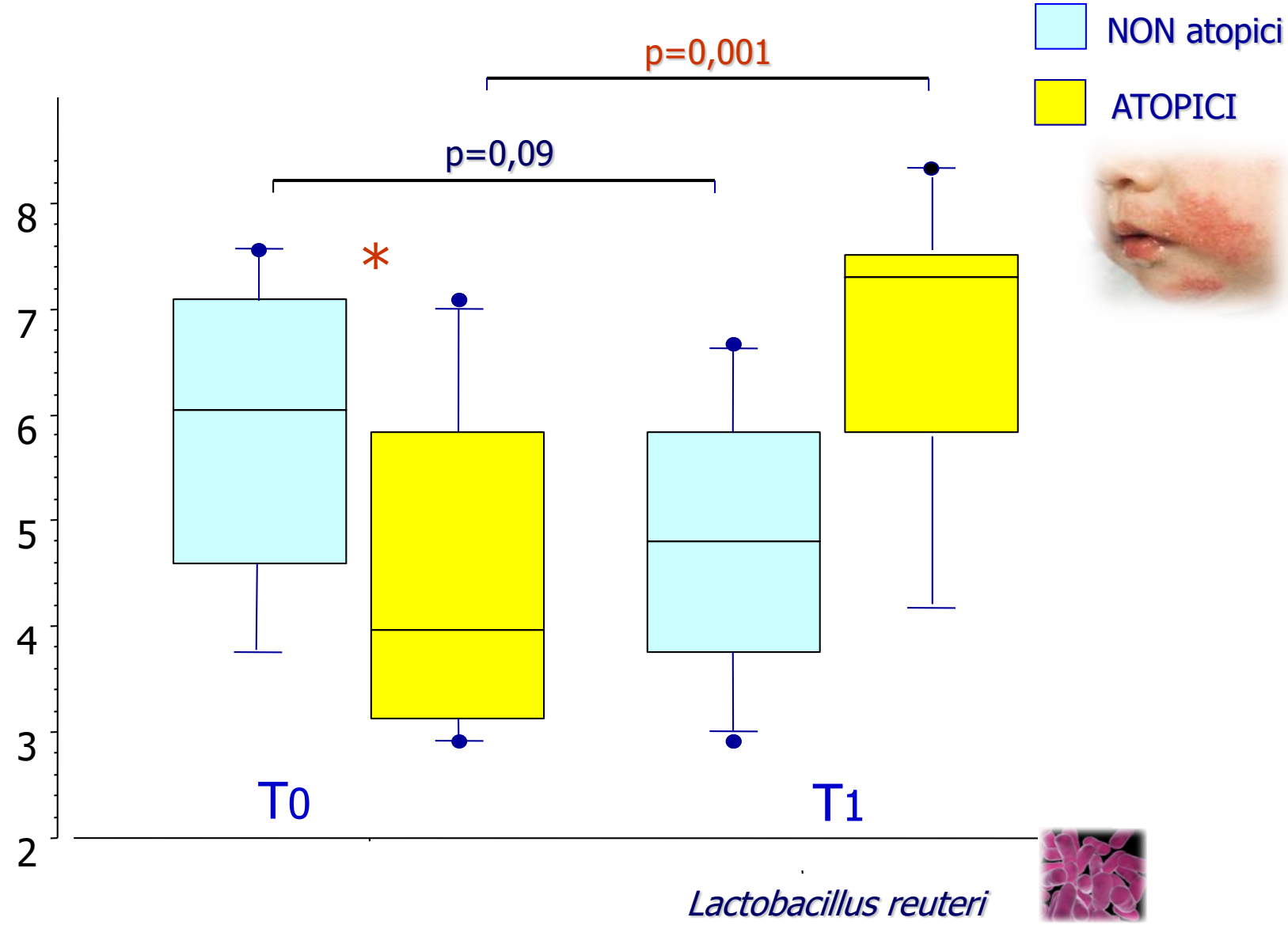
	Patients with AD receiving *Lactobacillus reuteri*	Patients with AD receiving placebo	Patients with nonatopic eczema receiving *Lactobacillus reuteri*	Patients with nonatopic eczema receiving placebo
T0	27 (21–44)	31 (23–50)	35 (23–47)	33 (27–50)
T1	25 (21–42)	27 (22–47)	31 (21–43)	34 (25–49)

After 8 weeks of treatment, no significant changes in the Severity Scoring Index Atopic Dermatitis Index mean values were observed in patients who received the probiotic supplementation compared with children who received placebo (Table 1).

IFN-γ nell'esalato condensato

IFN-γ
(pg/ml)

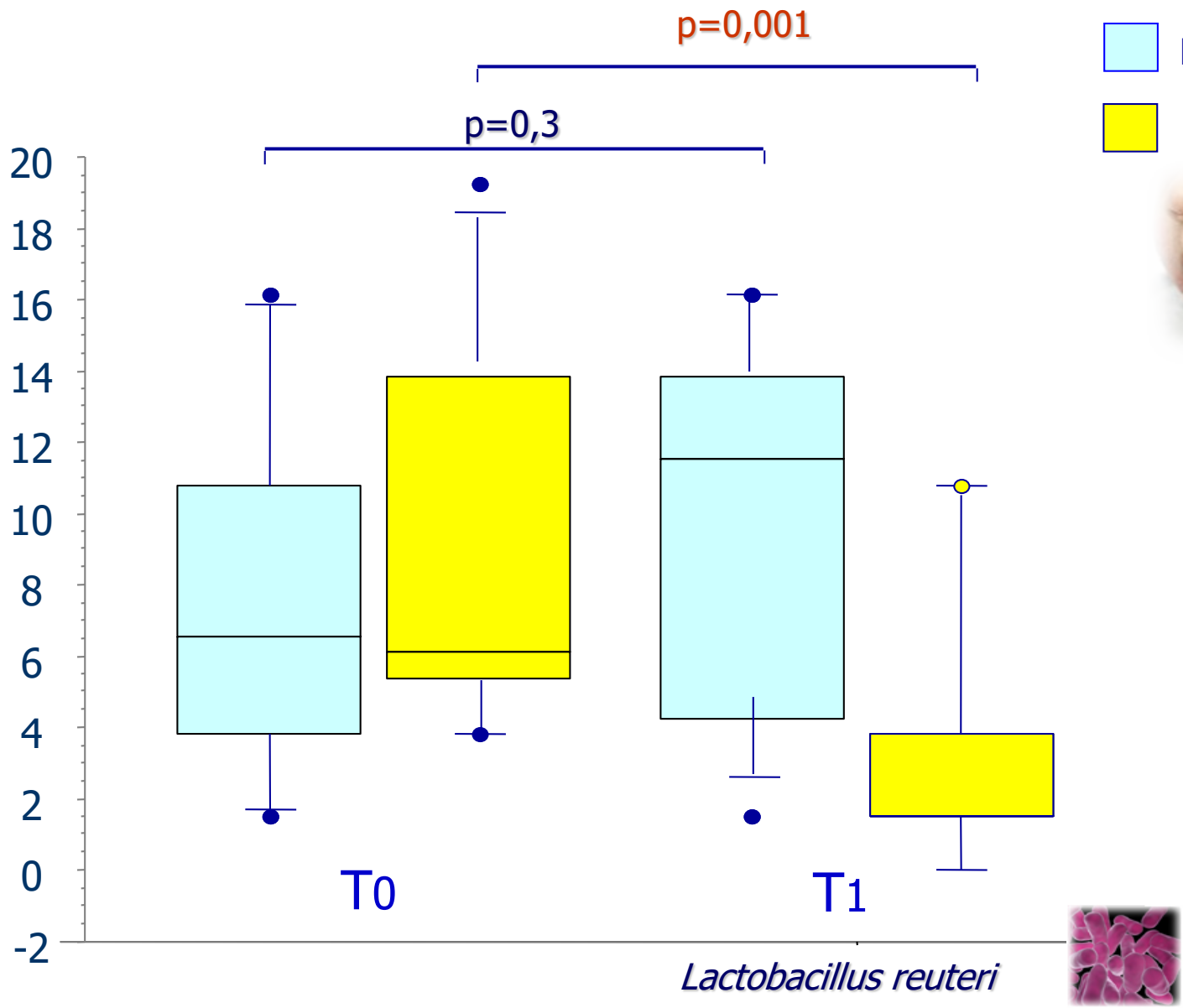
* p<0.03

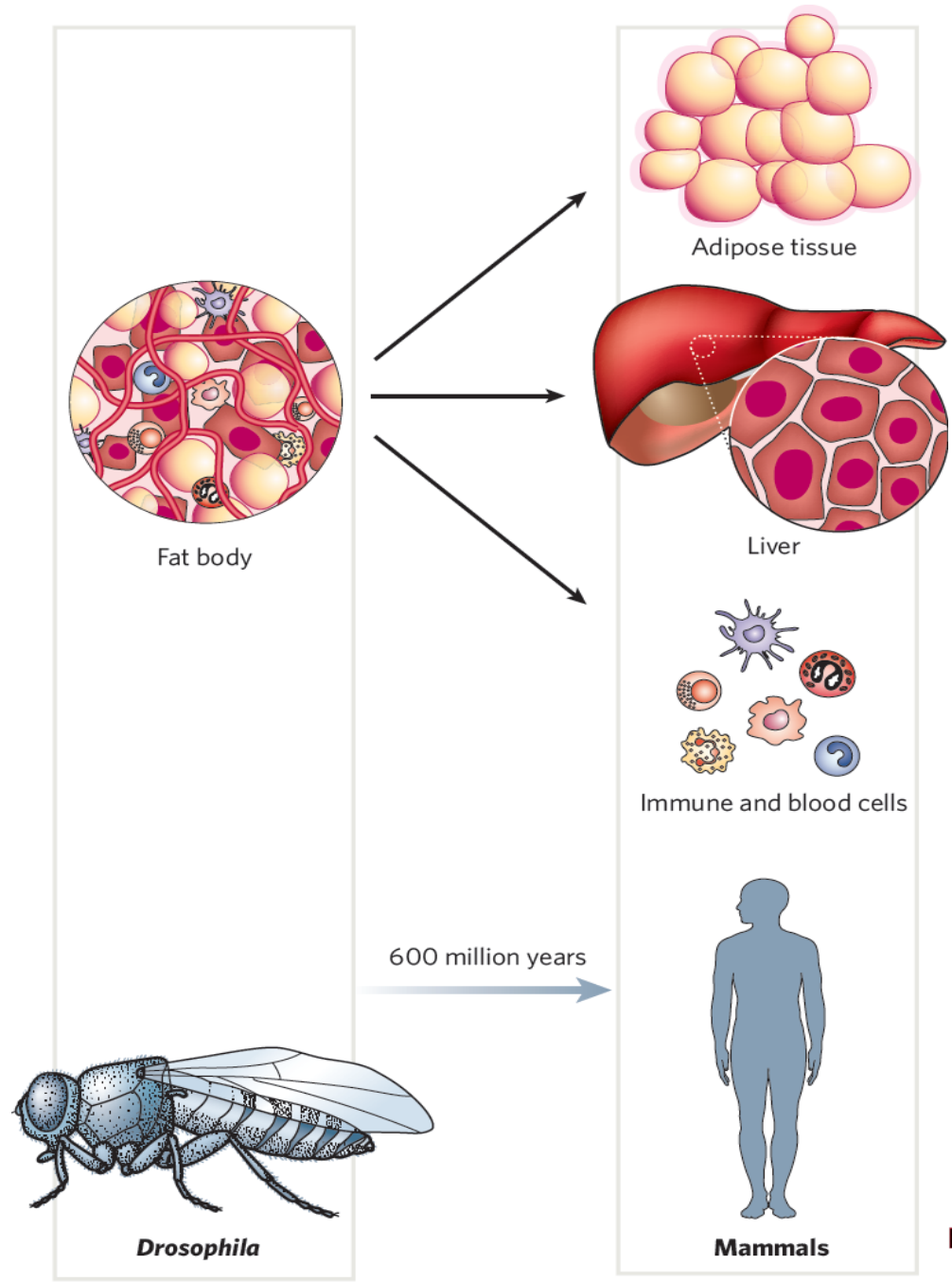


Lactobacillus reuteri

IL-4 nell'esalato condensato

IL-4
(pg/ml)

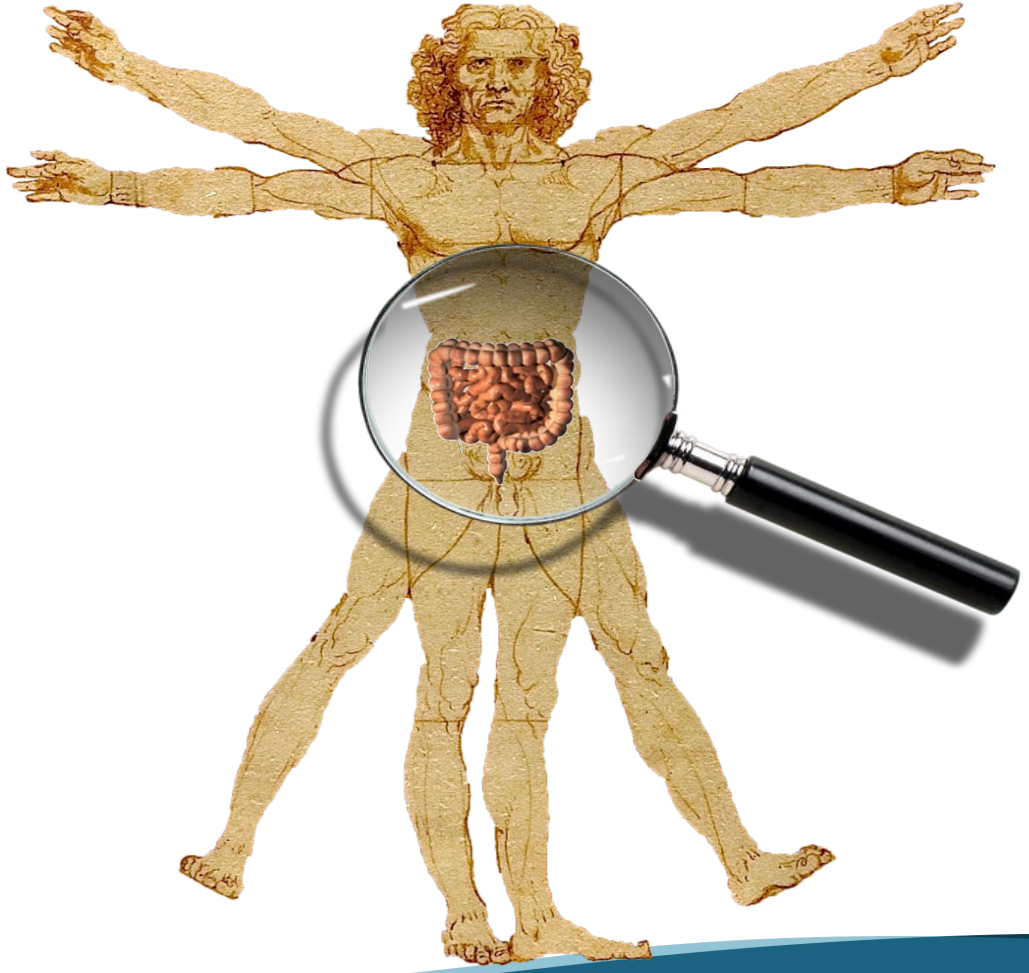


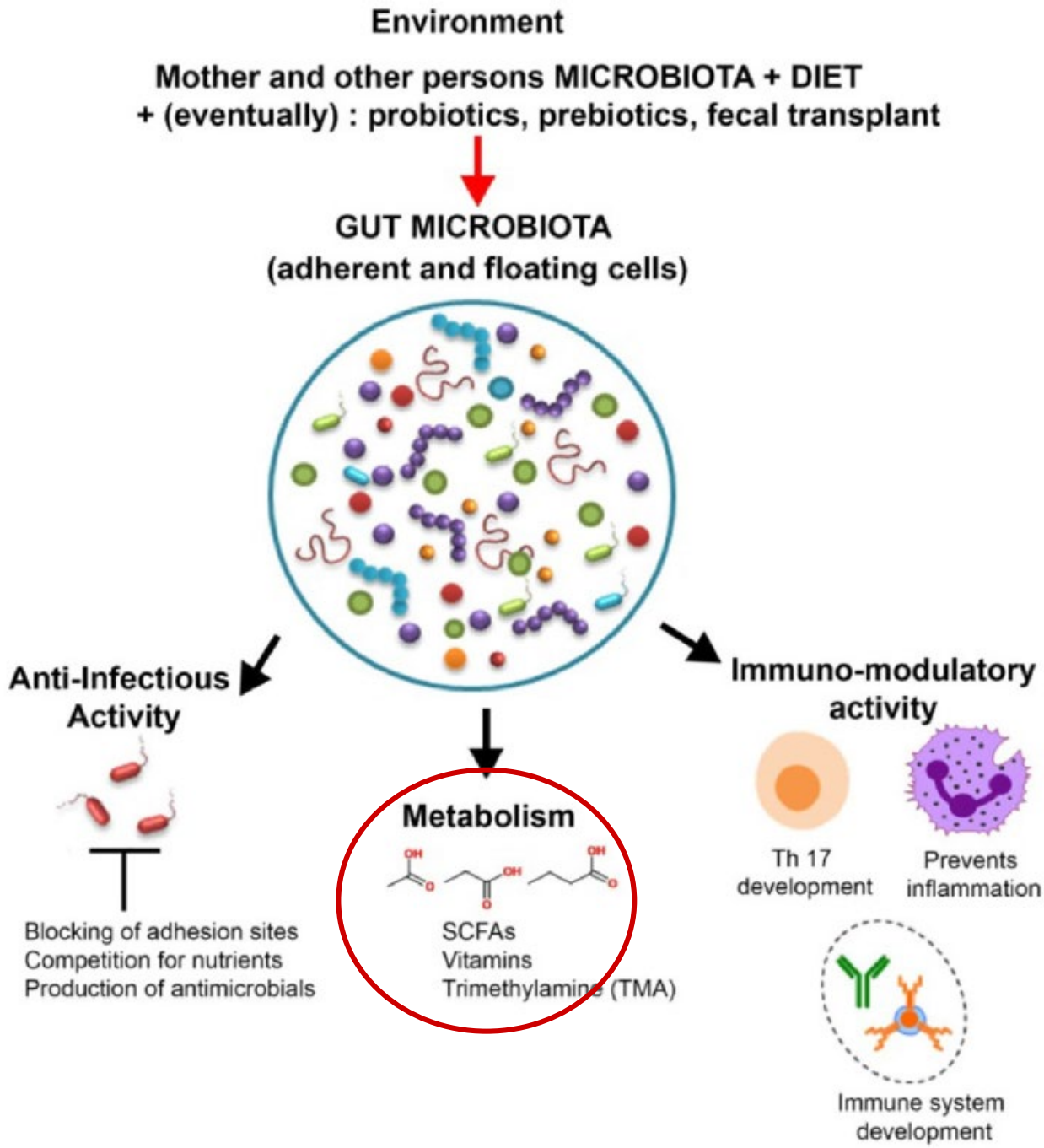


Gökhan S. Hotamisligil

NATURE|Vol 444|14 December 2006

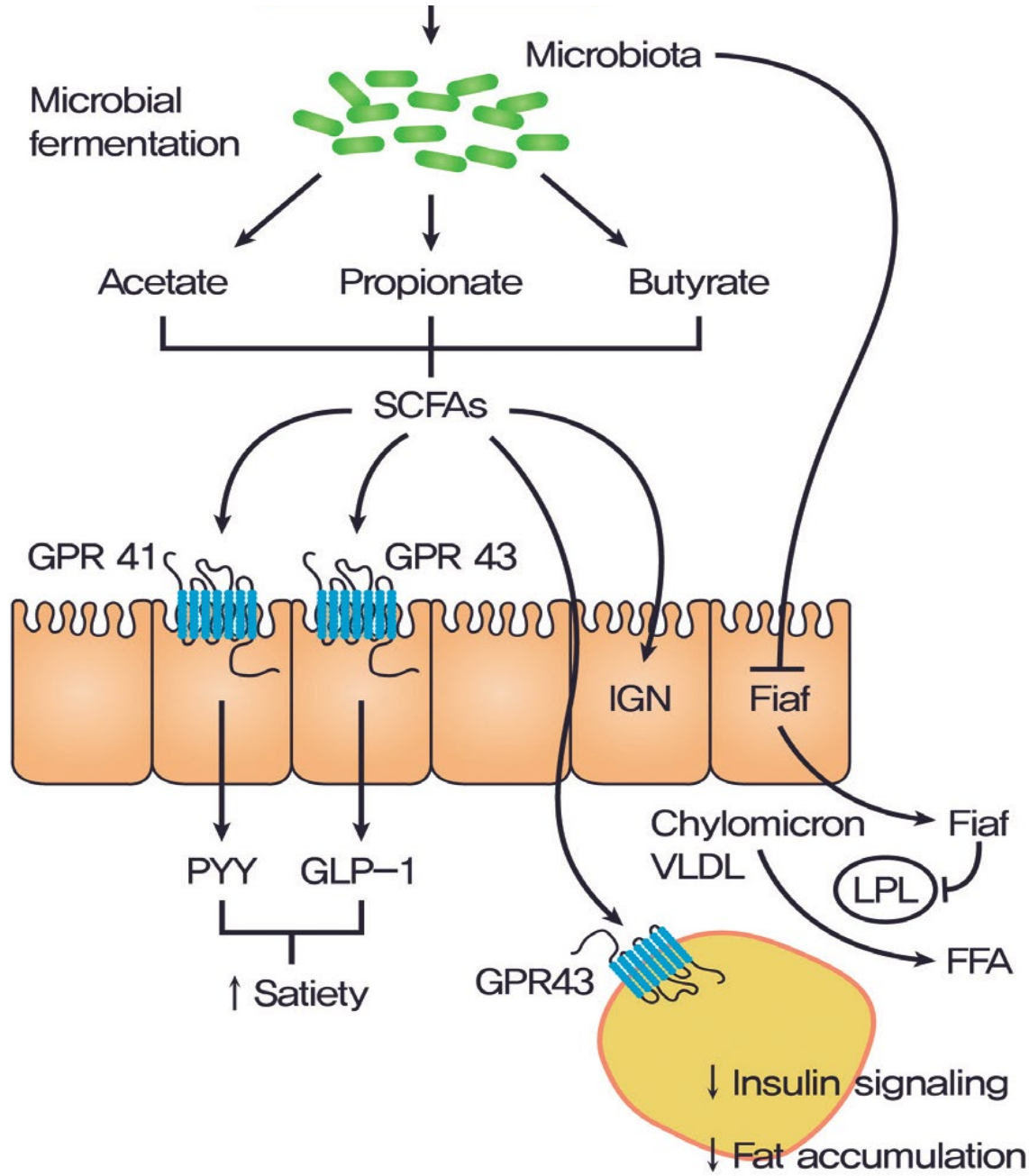
Il microbiota intestinale è un *organo batterico* **metabolicamente attivo**

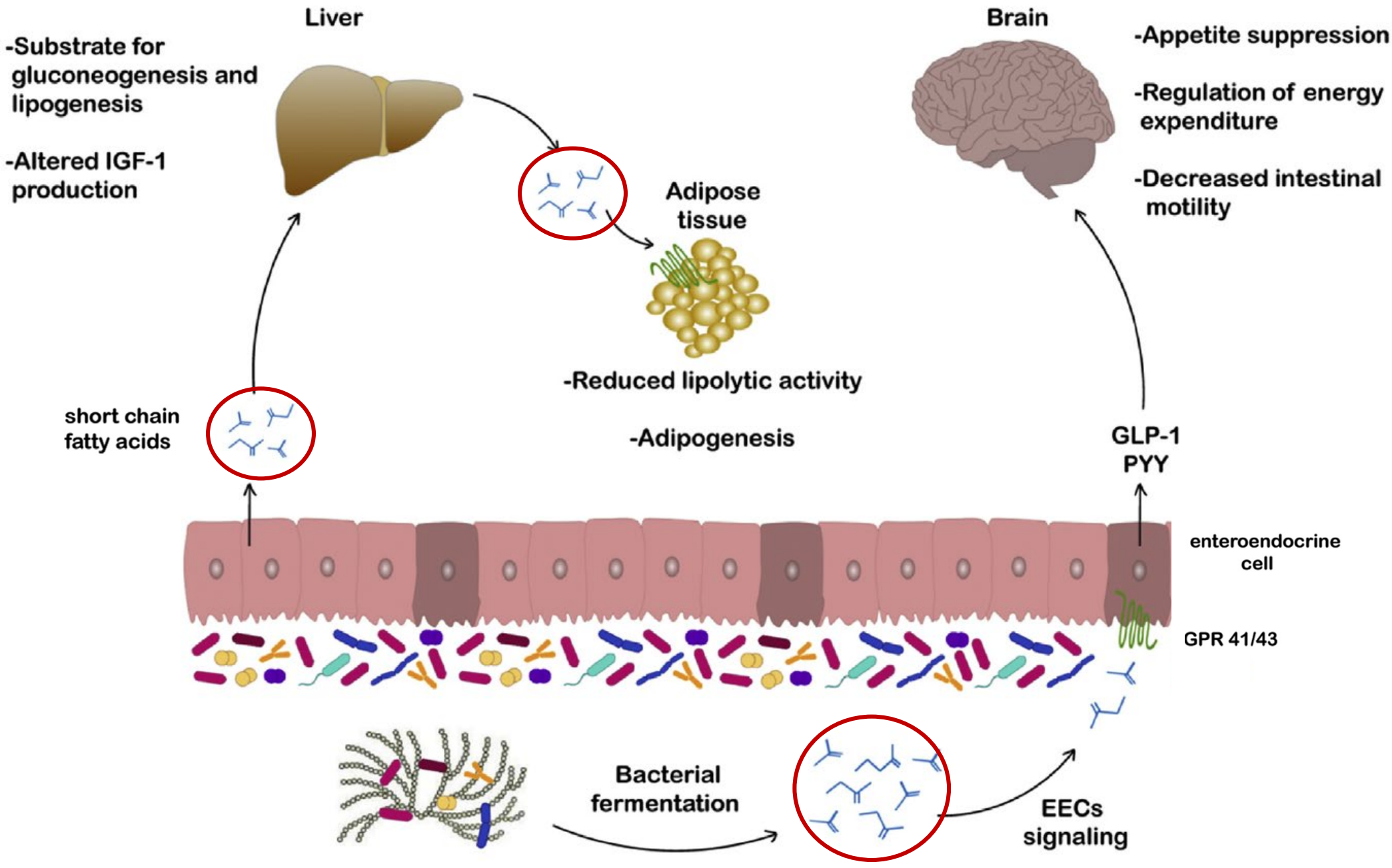




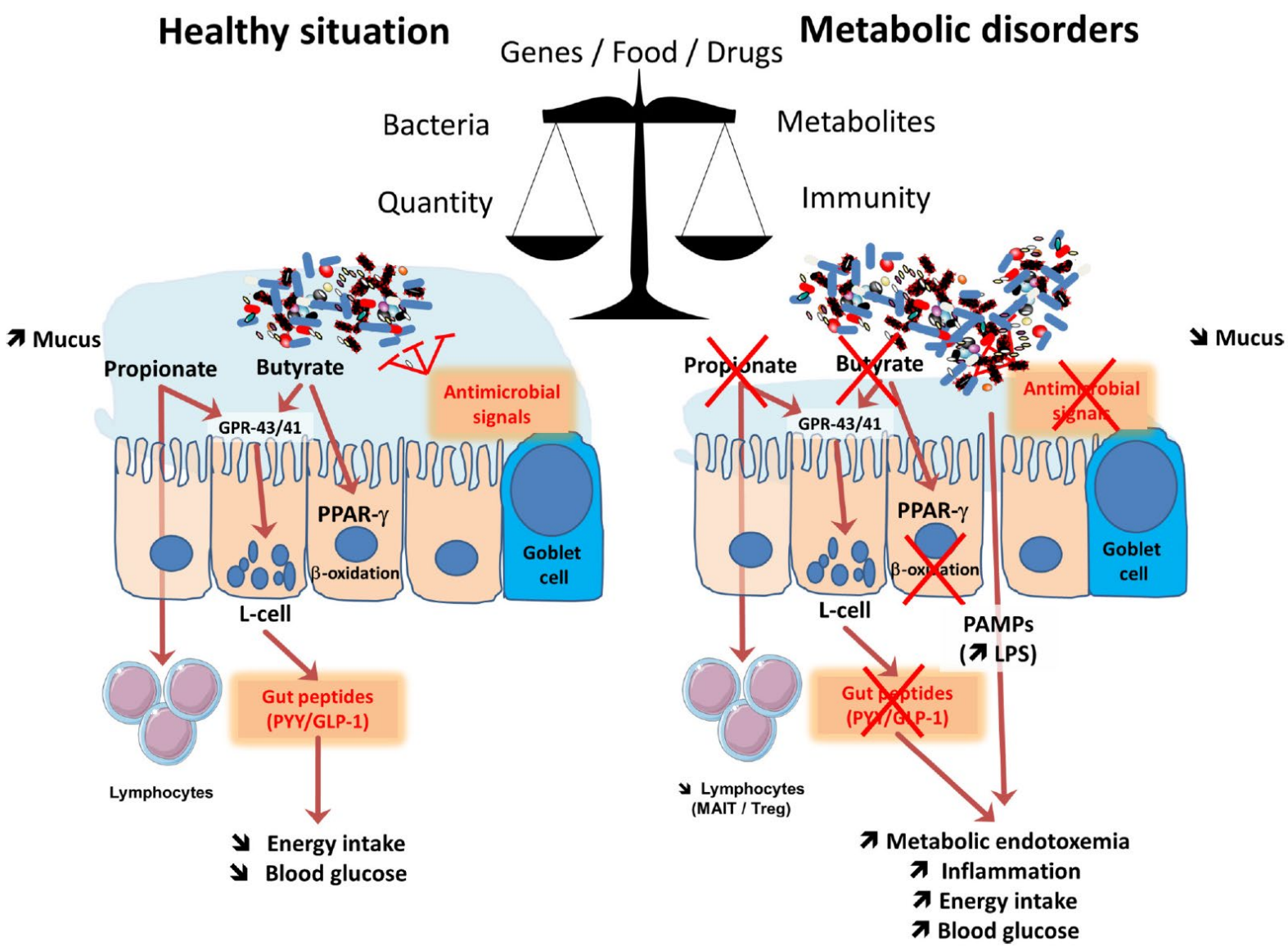
Veronica Lazar 2019

Dietary Fibers

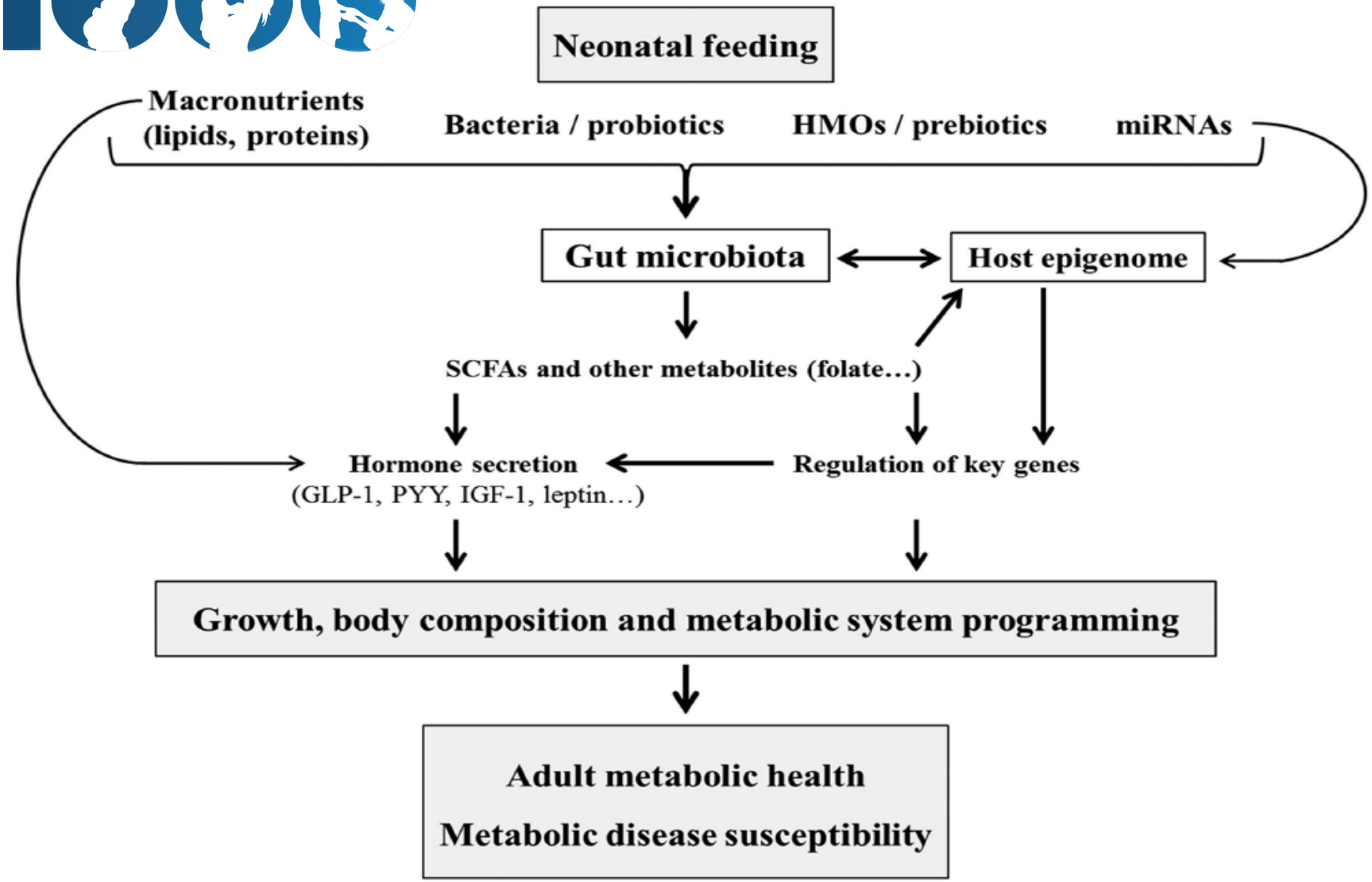




C.T. Pekmez et al. / Clinical Nutrition (2018)

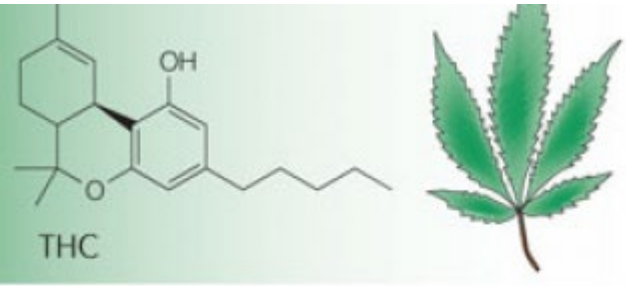


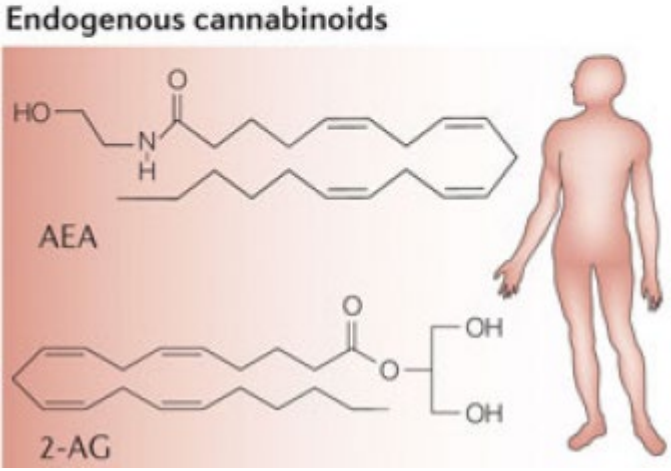
Cani PD. *Gut* 2018

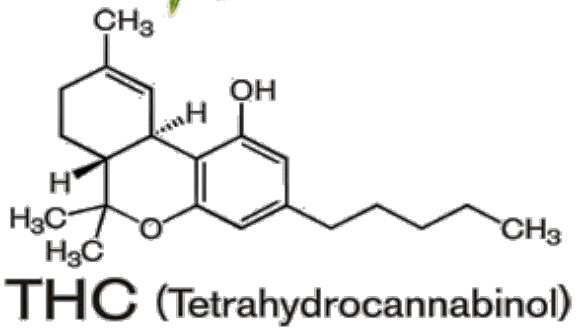


M. Lemaire *Journal of Developmental Origins of Health and Disease*, 2017,

THE **ENDOCANNABINOID** SYSTEM



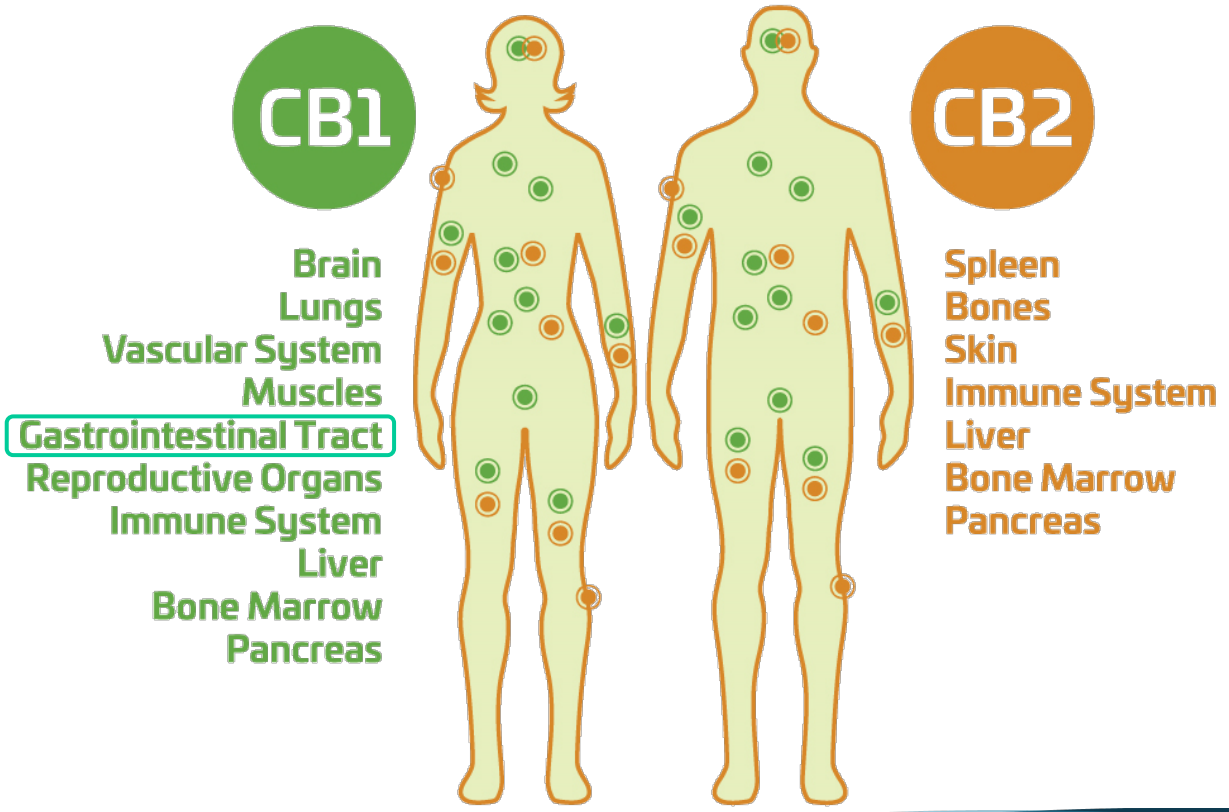




THC (Tetrahydrocannabinol)

THE **ENDOCANNABINOID** SYSTEM

Glucose metabolism: Focus on gut microbiota, the endocannabinoid system and beyond P.D. Cani & Diabetes Metabolism

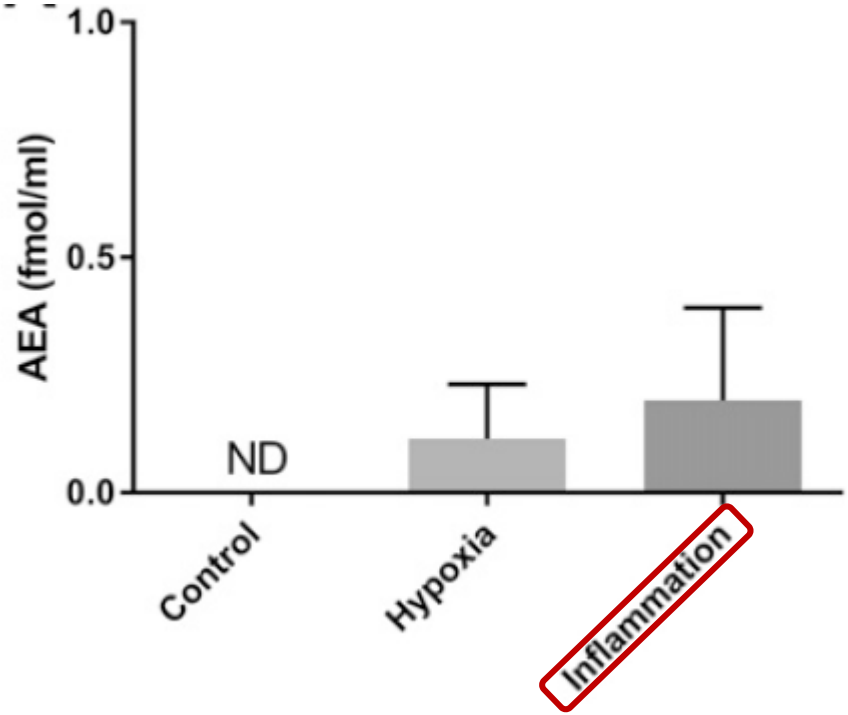


The role of CB_1 in intestinal permeability and inflammation

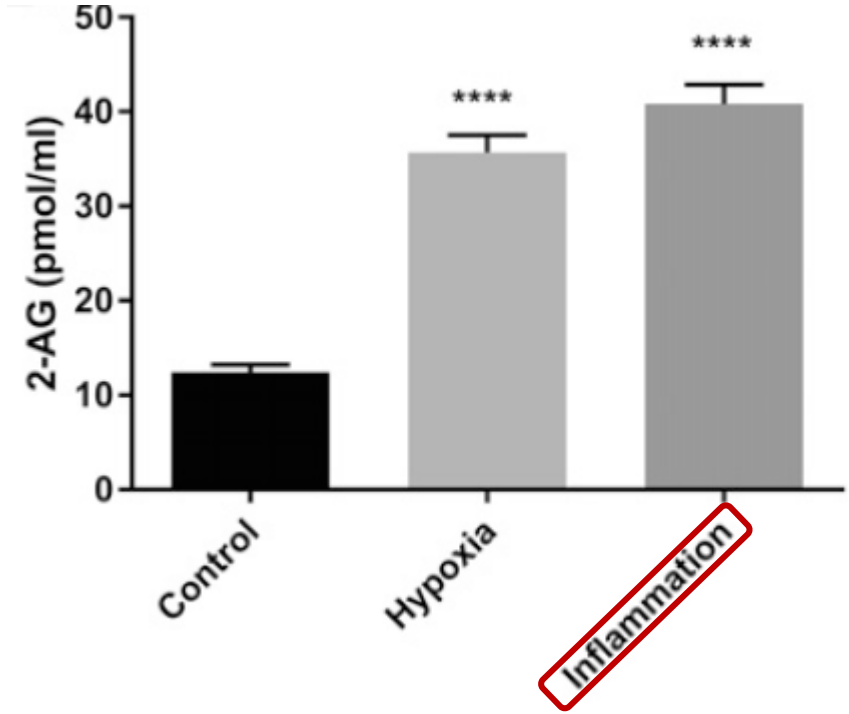
The FASEB Journal 2017

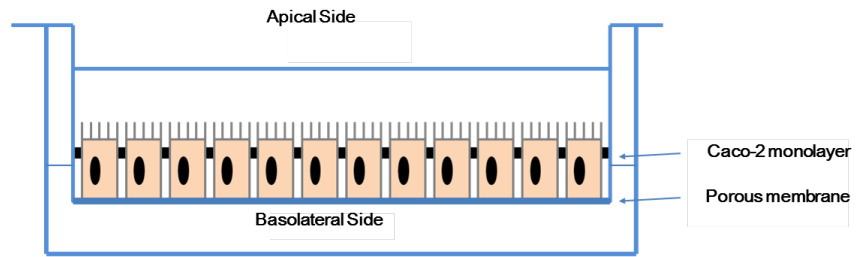
Mustafa A. Karwad,* Daniel G. Couch,* Elena Theophilidou,* Sarir Sarmad,† David A. Barrett,†

endogenous production of **anandamide (AEA)**



endogenous production of **2-arachidonoyl glycerol (2-AG)**





The role of CB_1 in intestinal permeability and inflammation

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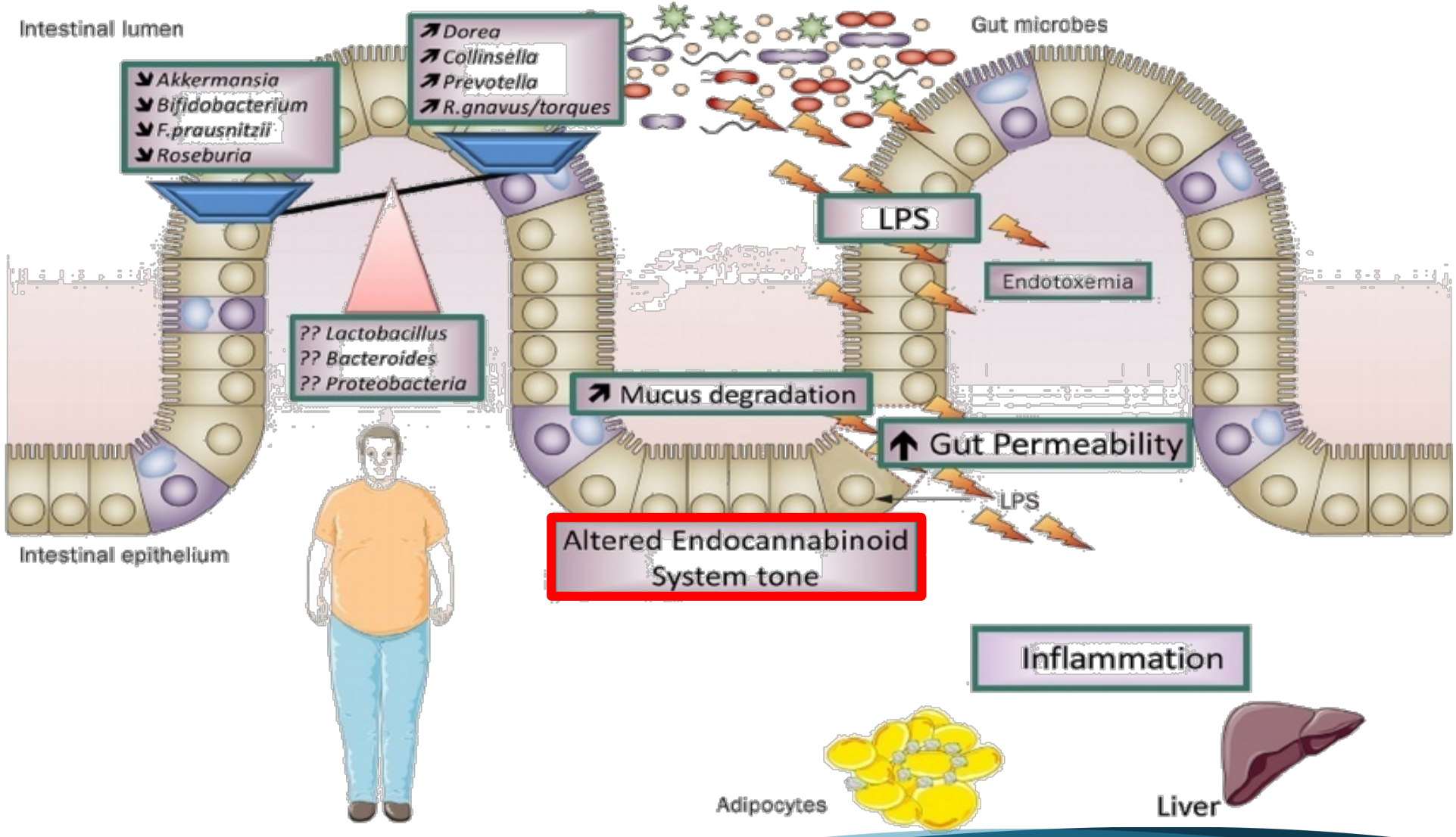
This suggests that there may be an association between high levels of AEA and 2-AG, acting at the CB_1 receptor in response to an inflammatory stimulus, leading to increased gut permeability and its secondary consequences, such as translocation of bacterial and LPS, but also simultaneously decreasing the inflammatory response.

Dysbiosis

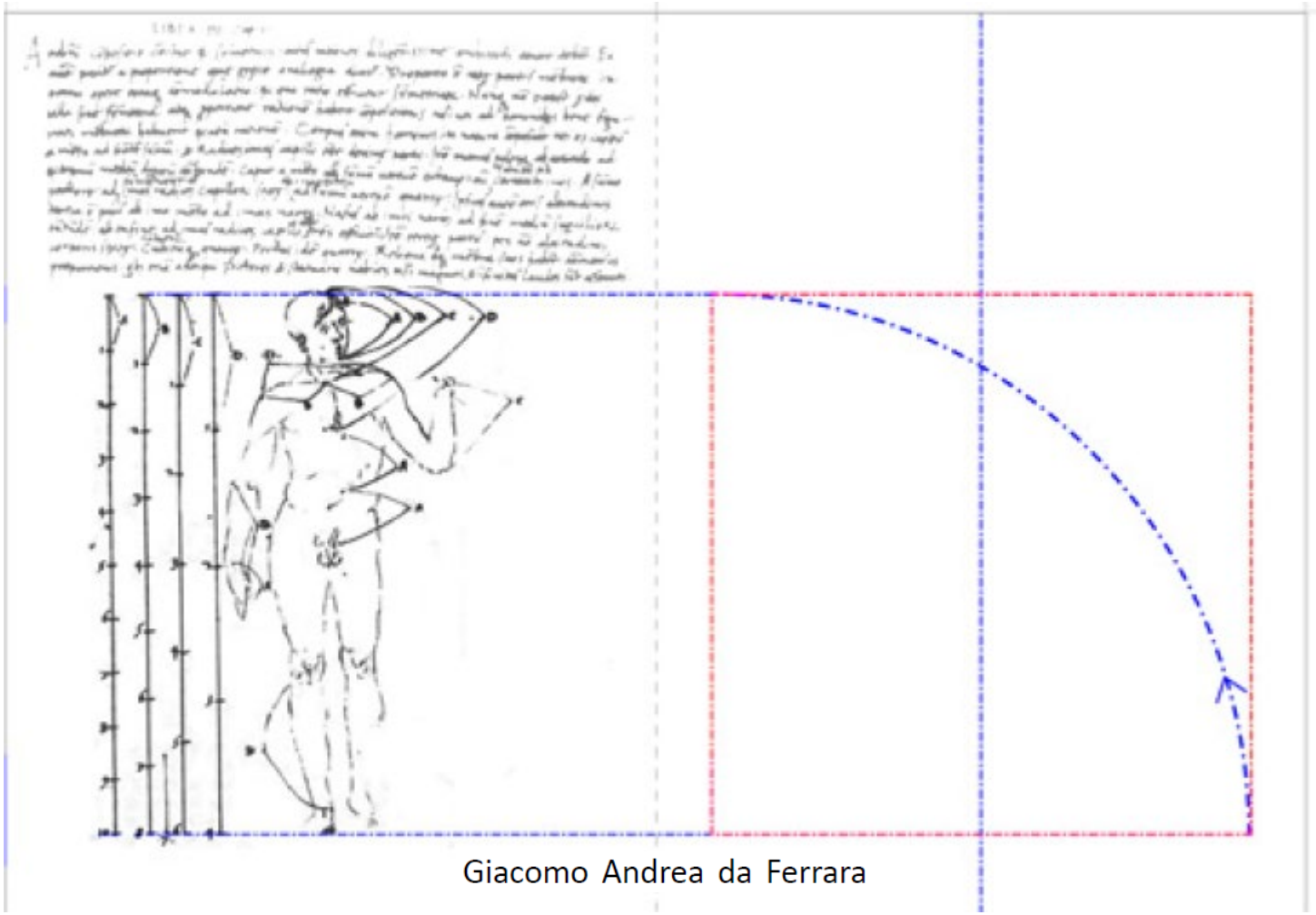

Intestinal lumen
↘ Akkermansia
↘ Bifidobacterium
↘ F.prausnitzii
↘ Roseburia
↗ Dorea
↗ Collinsella
↗ Prevotella
↗ R.gnavus/torques
?? Lactobacillus
?? Bacteroides
?? Proteobacteria
Gut microbes
LPS
Endotoxemia
↗ Mucus degradation
↑ Gut Permeability
LPS
Intestinal epithelium
Altered Endocannabinoid System tone
Inflammation
Adipocytes
Liver

città che dovrebbe avere le stesse *ragion, misura e forma* del corpo umano

Codice Torinese Saluzzaino

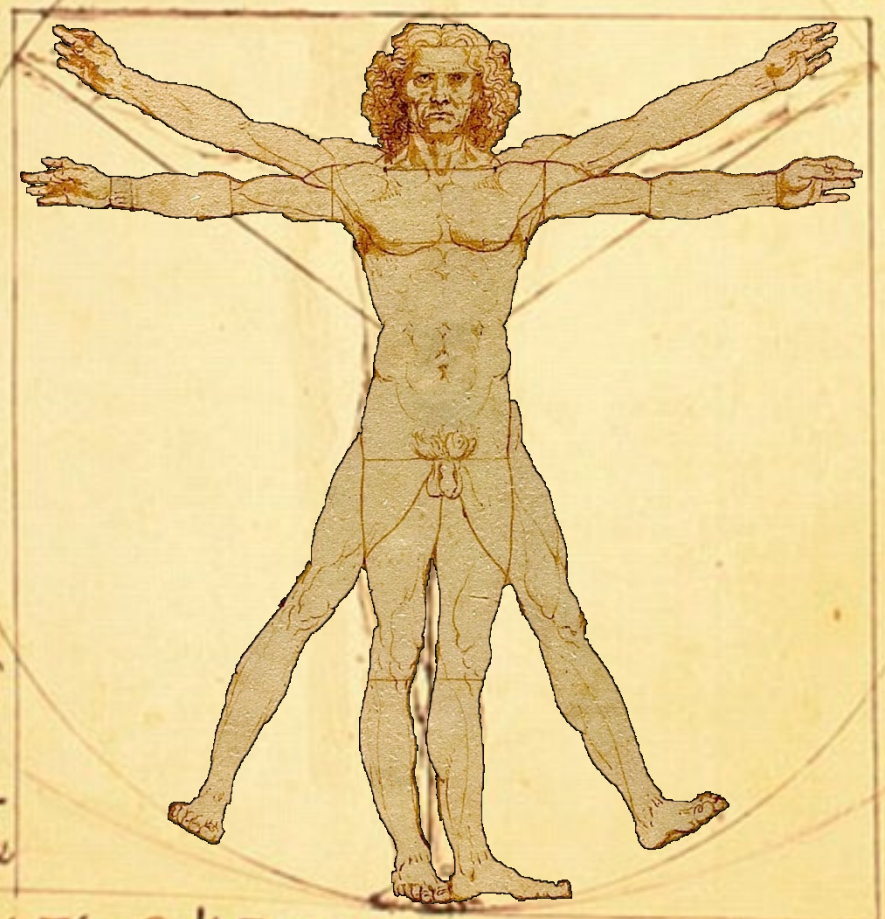
Francesco di Giorgio Martini

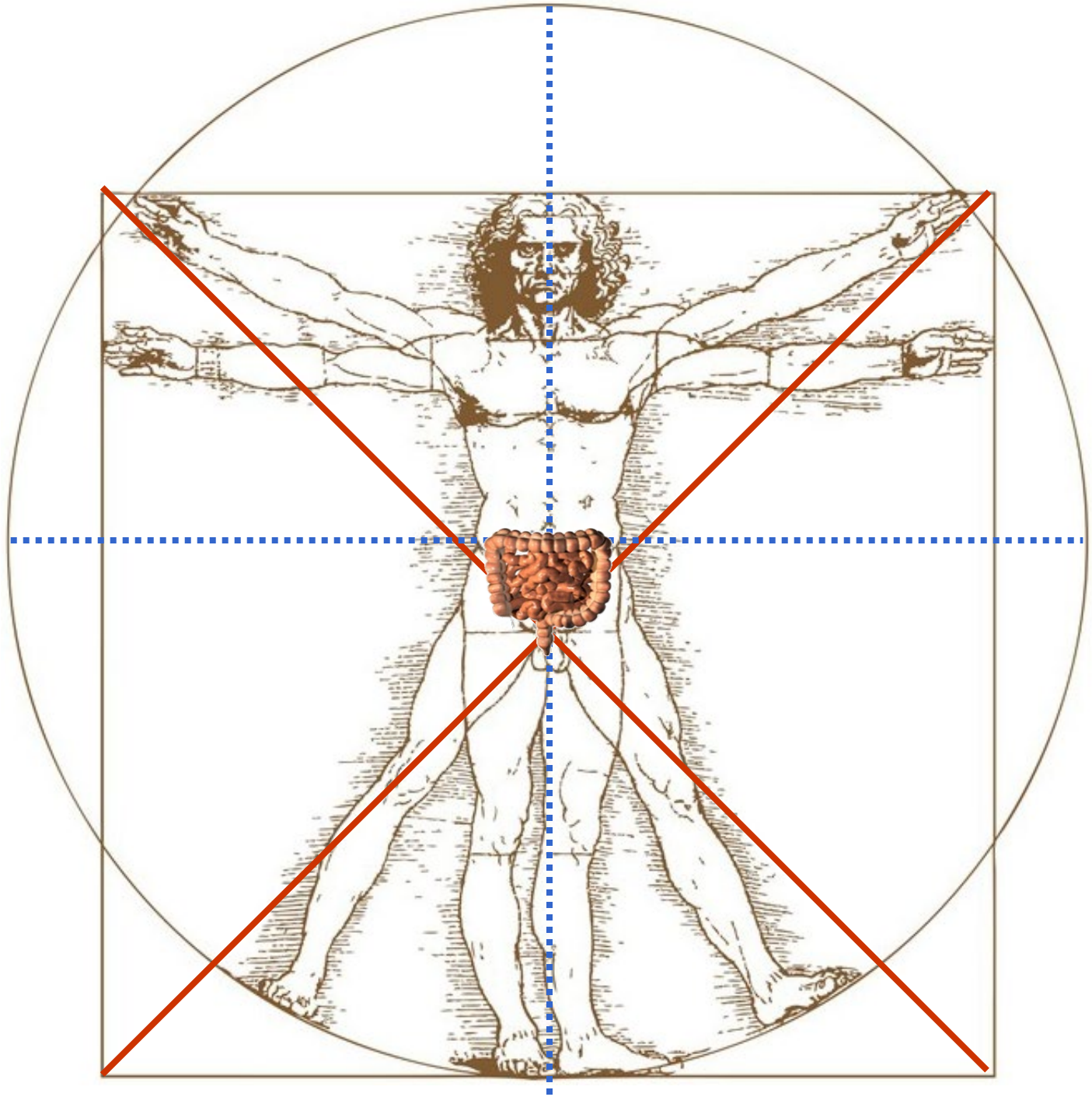
At the origin of Leonardo's Ideal Man



Giacomo Andrea da Ferrara

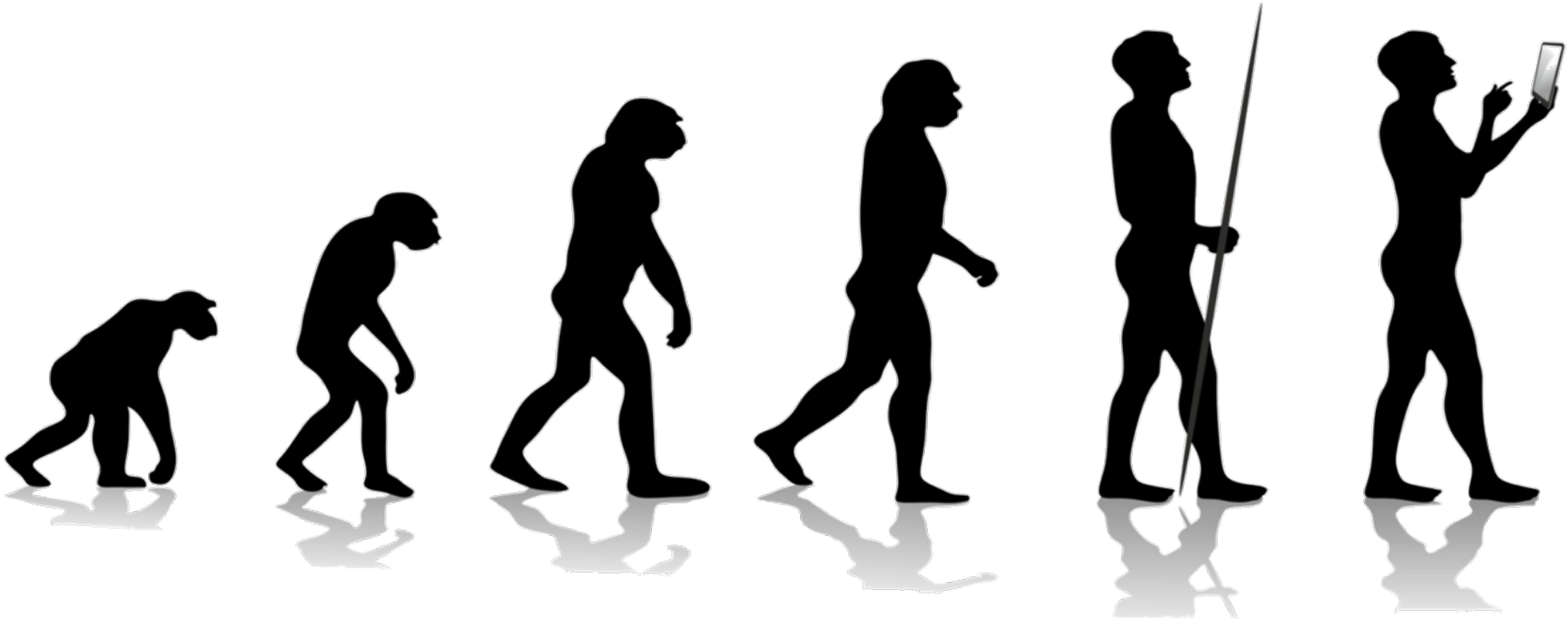
Giacomo Andrea da Ferrara

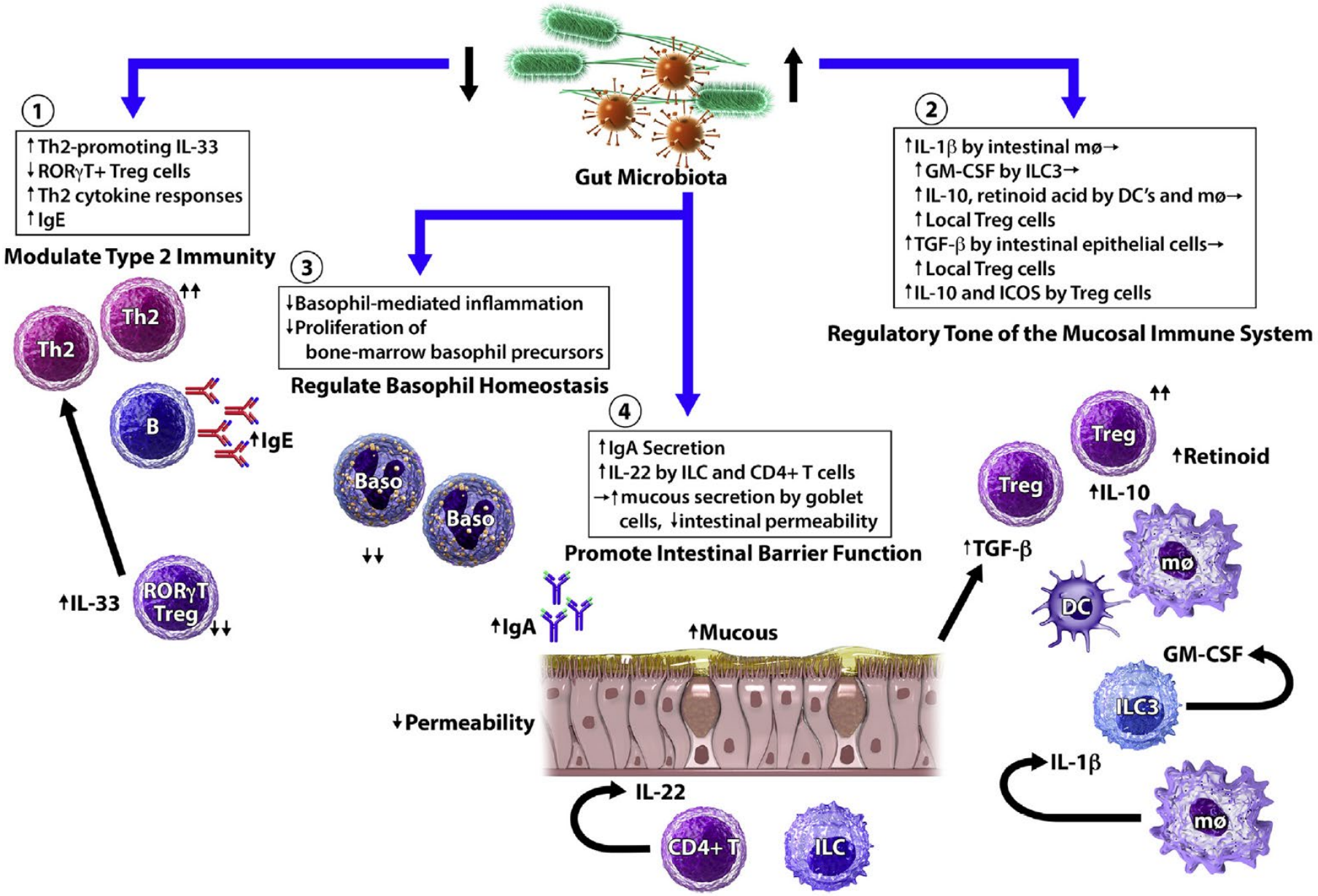




"Da quando si è eretto sugli arti posteriori,
l'uomo non ha saputo più riacquistare l'equilibrio."

Stanislaw Jerzy Lec




Gut Microbiota
1
↑Th2-promoting IL-33
↓RORγT+ Treg cells
↑Th2 cytokine responses
↑IgE
Modulate Type 2 Immunity
Th2
Th2
B
↑IgE
↑IL-33
RORγT Treg
3
↓Basophil-mediated inflammation
↓Proliferation of bone-marrow basophil precursors
Regulate Basophil Homeostasis
Baso
Baso
2
↑IL-1β by intestinal mø→ ↑GM-CSF by ILC3→
↑IL-10, retinoid acid by DC's and mø→ ↑Local Treg cells
↑TGF-β by intestinal epithelial cells→ ↑Local Treg cells
↑IL-10 and ICOS by Treg cells
Regulatory Tone of the Mucosal Immune System
4
↑IgA Secretion
↑IL-22 by ILC and CD4+ T cells
→↑mucous secretion by goblet cells, ↓intestinal permeability
Promote Intestinal Barrier Function
↑IgA
↑Mucous
↓Permeability
IL-22
CD4+ T
ILC
Treg
Treg
↑Retinoid
↑IL-10
↑TGF-β
DC
mø
GM-CSF
ILC3
IL-1β
mø

MICROBIOME DEVELOPMENT

UTERUS

Sparse colonization of placental tissue and amniotic fluid with the commensal bacteria from the mother.
Influence of maternal health conditions and immune status: obesity, gestational diabetes mellitus, atopic diseases.

DELIVERY

Determines the composition of the pioneering microbes:

- Vaginal delivery: *Lactobacillus, Prevotella, Enterobacteriaceae.* Resembles the vaginal microbiota
- C-section: *Staphylococcus, Corynebacterium, Propionibacterium.* Resembles the skin microbiota and show delayed *Bacteroidetes* and *Bifidobacterium* colonization.

BREASTFEEDING

Microbial transfer from BM: *Staphylococcus, Streptococcus, Propionibacterium, etc.*

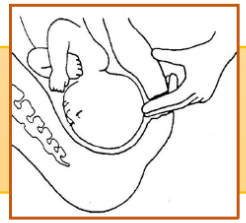
- **Increases anaerobic organisms**: *Bifidobacterium, Lactobacillus, Veillonella, etc.*

HMO support the growth of beneficial bacteria in the colon.

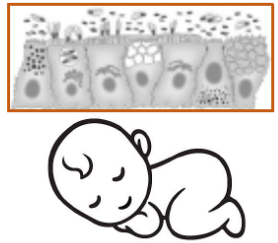
ENVIRONMENT

- Number of **siblings**
- Furred **pet** exposure
- Rural vs urban **living areas**
- Household **size**
- **Daycare** attendance

Antibiotics intake: microbial depletion and altered immune system development

GUT IMMUNITY MATURATION



Probiotics intake: selective bacterial enrichment

IMMUNE MATURATION

Molecular signals from the mother contribute to the expansion of intestinal innate immune populations and the secretion of antibodies into the intestinal lumen, as shown in mice models. The information about these mechanisms in human studies is still lacking.

C-section associated to immune system disorders in the child: atopic diseases, obesity, diabetes, etc.
Effect of the delivery mode on the immune system maturation is still not well described.

- **BM bacteria**: maintain colonization resistance against pathogens.
- **IgA, IgM and IgG:** protect the neonatal intestinal mucosal surface and limit inflammation.
- **Antimicrobial proteins**: lactalbumin, lysozyme, lactoferrin.
- **Cytokines** that modulate inflammatory responses.
- **HMOs** inhibit pathogen binding to gut mucosa
- Other **protective/immune** modulating **compounds**: leukocytes, glysosilated proteins, CD14, etc.

- **Favors bacterial diversity** → appropriate immune maturation
- **Innate immune responsiveness**
- Specific allergen **sensitization/tolerance**