

XXX

CONGRESSO NAZIONALE
SOCIETÀ ITALIANA DI PEDIATRIA
PREVENTIVA E SOCIALE



BAMBINI DI IERI, OGGI E DOMANI...
LA NOSTRA CARE, IL NOSTRO CUORE

TEATRO DI ORTIGIA • 7 - 10 GIUGNO 2018
SIRACUSA

IL RUOLO DELLA VITAMINA D E DEI PROBIOTICI NELLA
IMMUNO-MODULAZIONE DELLA RISPOSTA ALLERGICA

**I meccanismi «patogenetici» del
Lattobacillus Reuteri DSM 17938**

Oliviero Rossi

SOD IMMUNOALLERGOLOGIA

Direttore Prof. F. Almerigogna

AZIENDA OSPEDALIERA UNIVERSITARIA

CAREGGI FIRENZE

IL MERCATO DEI PROBIOTICI IN ITALIA PRODOTTI SUL MERCATO > 1000



Nel periodo che va **da aprile 2016 a marzo 2017** il segmento ha sviluppato un valore totale di **fatturato di 353,4 milioni di euro** (+6,4% rispetto allo stesso periodo dell'anno precedente) per un totale di **25,7 milioni di confezioni vendute** (+4,4%)

VALORE SCIENTIFICO ?

INTERESSE

PERPLESSITA'



Available online at www.sciencedirect.com

ScienceDirect

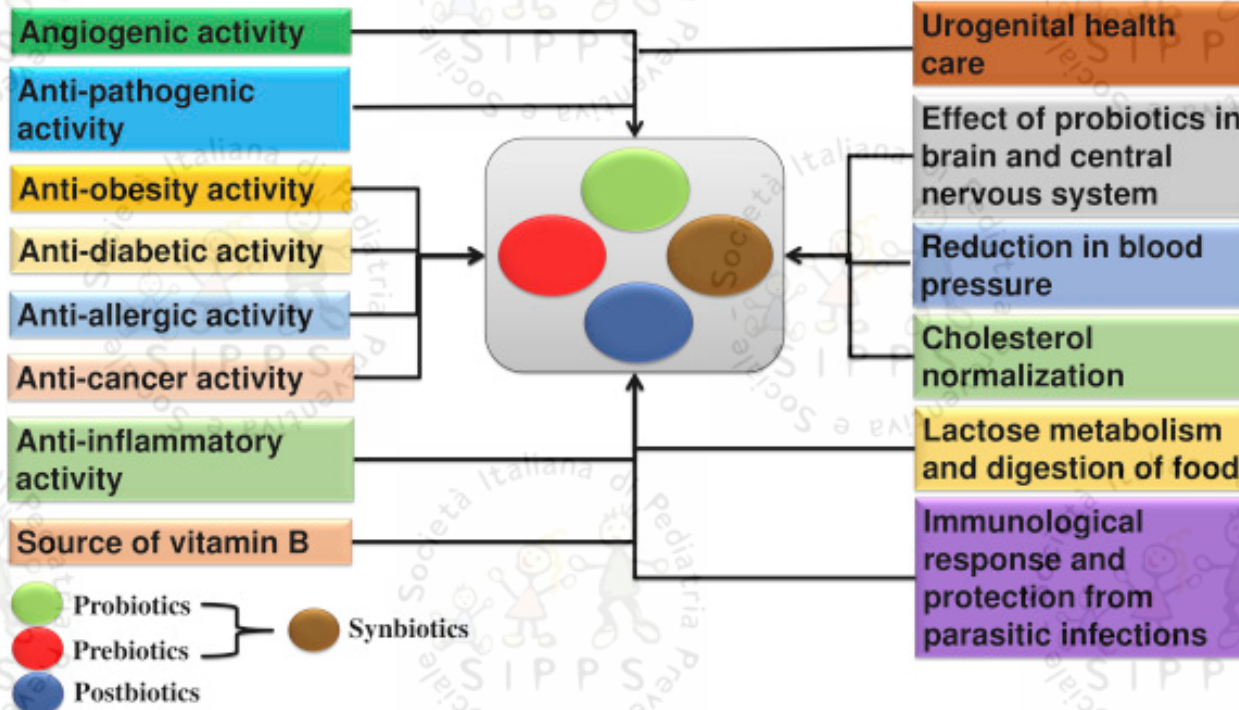
Journal homepage: www.jfda-online.com

Review Article

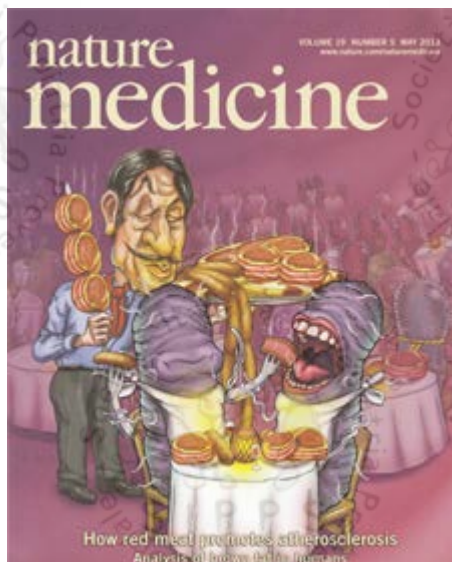
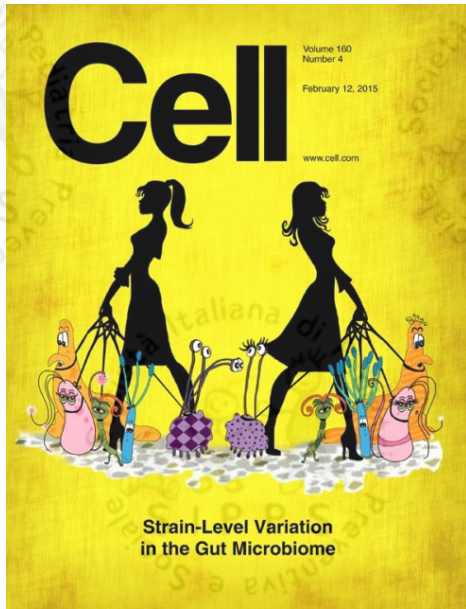
May 2018

Benefaction of probiotics for human health: A review

Rout George Kerry ^{a,1}, Jayanta Kumar Patra ^{b,1}, Sushanto Gouda ^c,
Yooheon Park ^b, Han-Seung Shin ^d, Gitishree Das ^{b,*}



«THE MICROBIOME REVOLUTION»



«THE MICROBIOME REVOLUTION»

JCI The Journal of Clinical Investigation

REVIEW SERIES INTRODUCTION: GUT MICROBIOME

The Journal of Clinical Investigation

Series Editor: Martin J. Blaser

The microbiome revolution

Martin J. Blaser

Department of Medicine and Microbiology, New York University Langone Medical Center, and New York Harbor Department of Veterans Affairs Medical Center, New York, New York, USA.

J Clin Invest. 2014;124(10):4162–4165. |

Microbial contributions to the development of immunity

Microbial contributions to the pathogenesis of chronic inflammatory diseases

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., Editor

The Microbiome and Systemic Lupus Erythematosus

James T. Rosenbaum, M.D., and Gregg J. Silverman, M.D.

- **How can it be that such a repugnant substance, feces, is also the key to our well-being?**
- **Fecal bacteria are essential to life, and humans are not alone in their dependence on the microbial world. Humans also depend on microbiota.**
- **The bacteria in our intestine not only dispose of waste but also educate the immune system, regulate levels of neurotransmitters, and synthesize essential nutrients such as vitamin K.**
- **Disruption (or dysbiosis) of this otherwise balanced ecosystem may result in disease; correction of dysbiosis may prevent disease.**

Biodiversity

Definition: Variety of different species.



© Can Stock Photo - asp29436946

Exposures during human evolution

Situation in modern urban centre

Helminths

Gut and non-gut (blood)

LOST

Ectoparasites

Fleas, lice, mites, ticks

MOSTLY LOST

Carrier states

Salmonella, hepatitis A virus, *H. pylori*, TB, toxoplasma

MOSTLY LOST

Microbiota of other humans:
skin, gut, airway,
oropharyngeal, genitourinary

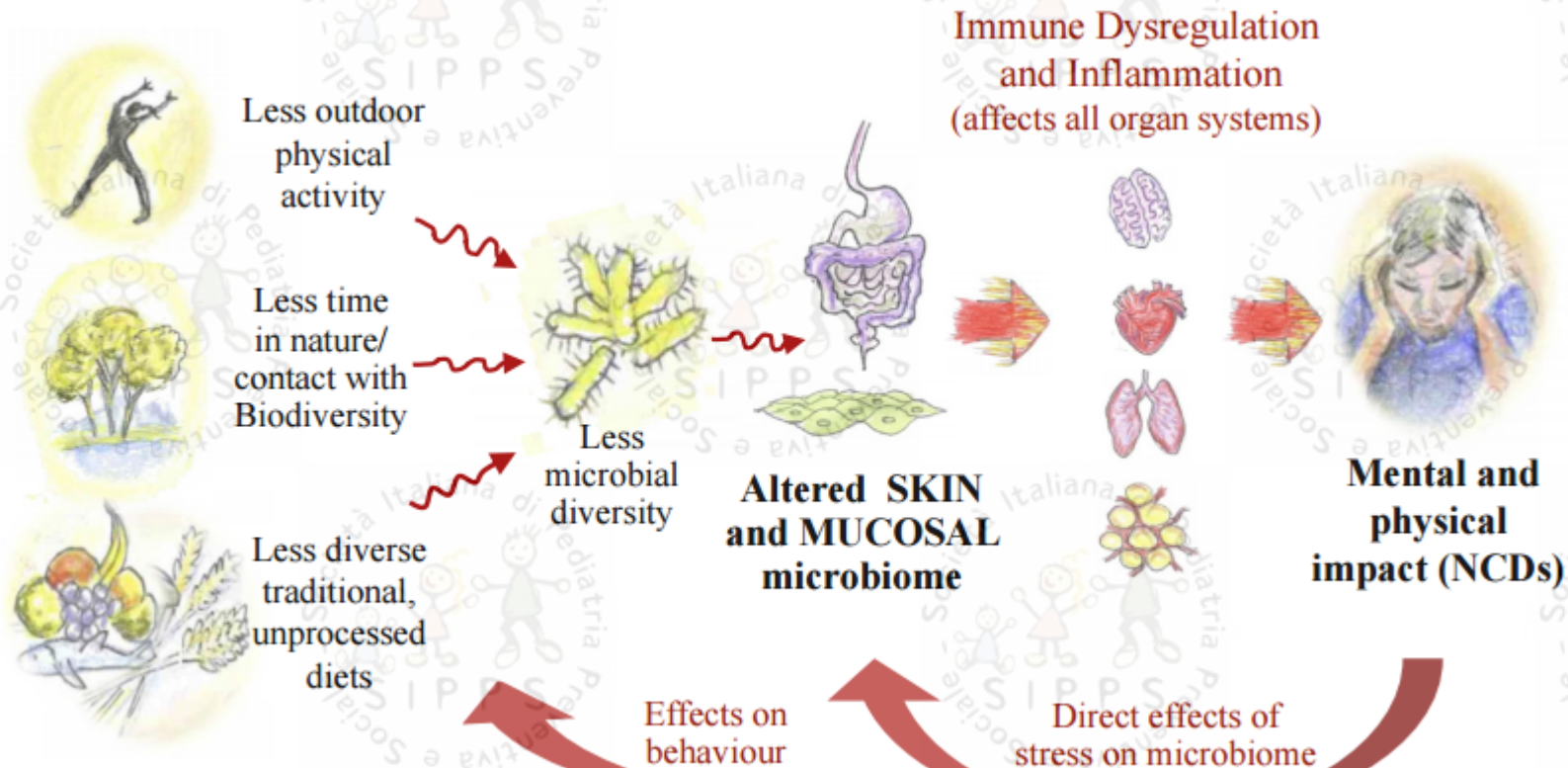
DIMINISHED
diversity

Microbiota of natural
environment: animals, soil,
air, plants (rhizosphere,
phyllosphere)

VARIABLE loss

Environmental Changes, Microbiota, and Allergic Diseases

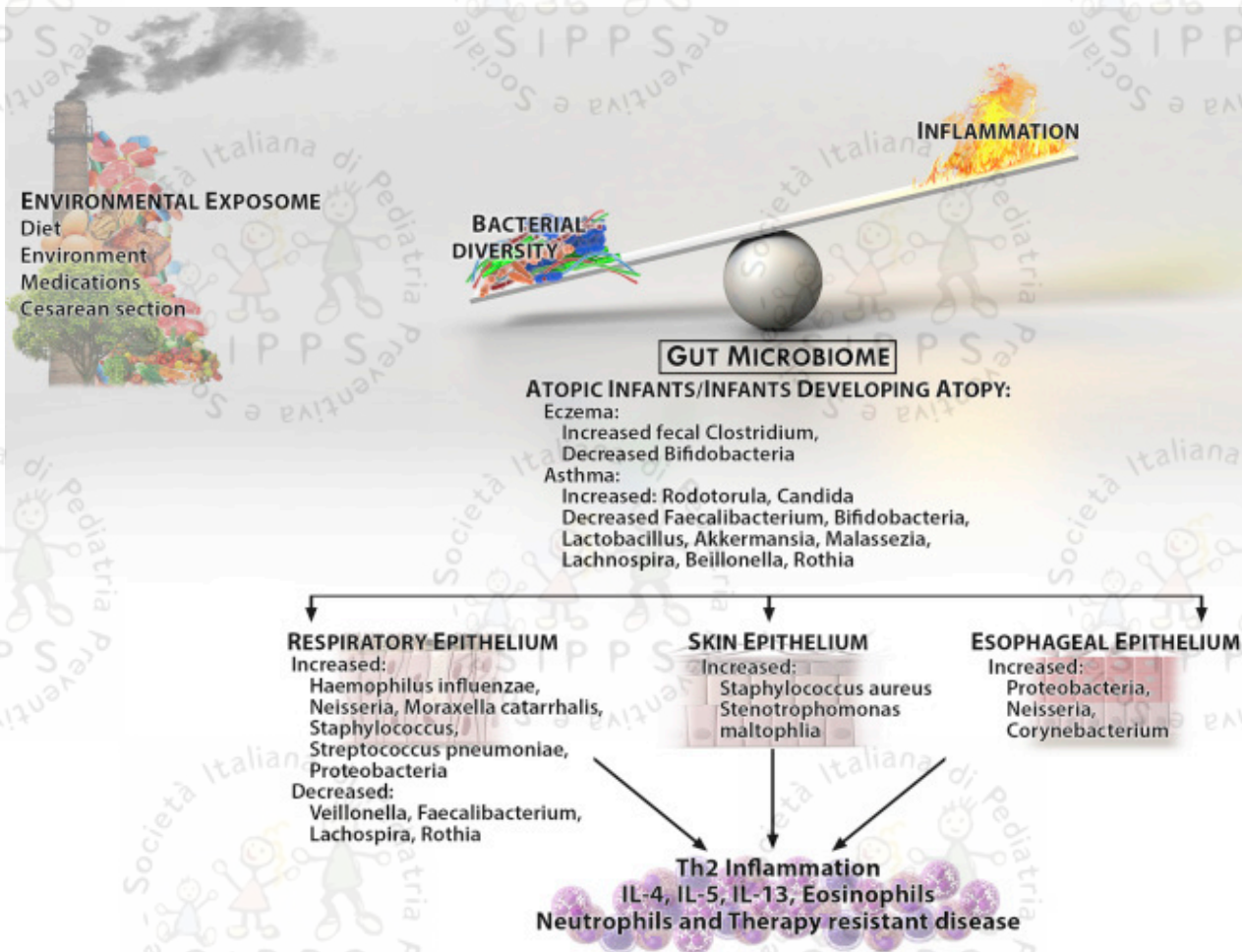
Biodiversity Associated Lifestyle Factors: A Pathway to Inflammation and NCDs



Lifestyle factors can contribute to or diminish microbial diversity.
Many aspects of modernity promote dysbiosis.

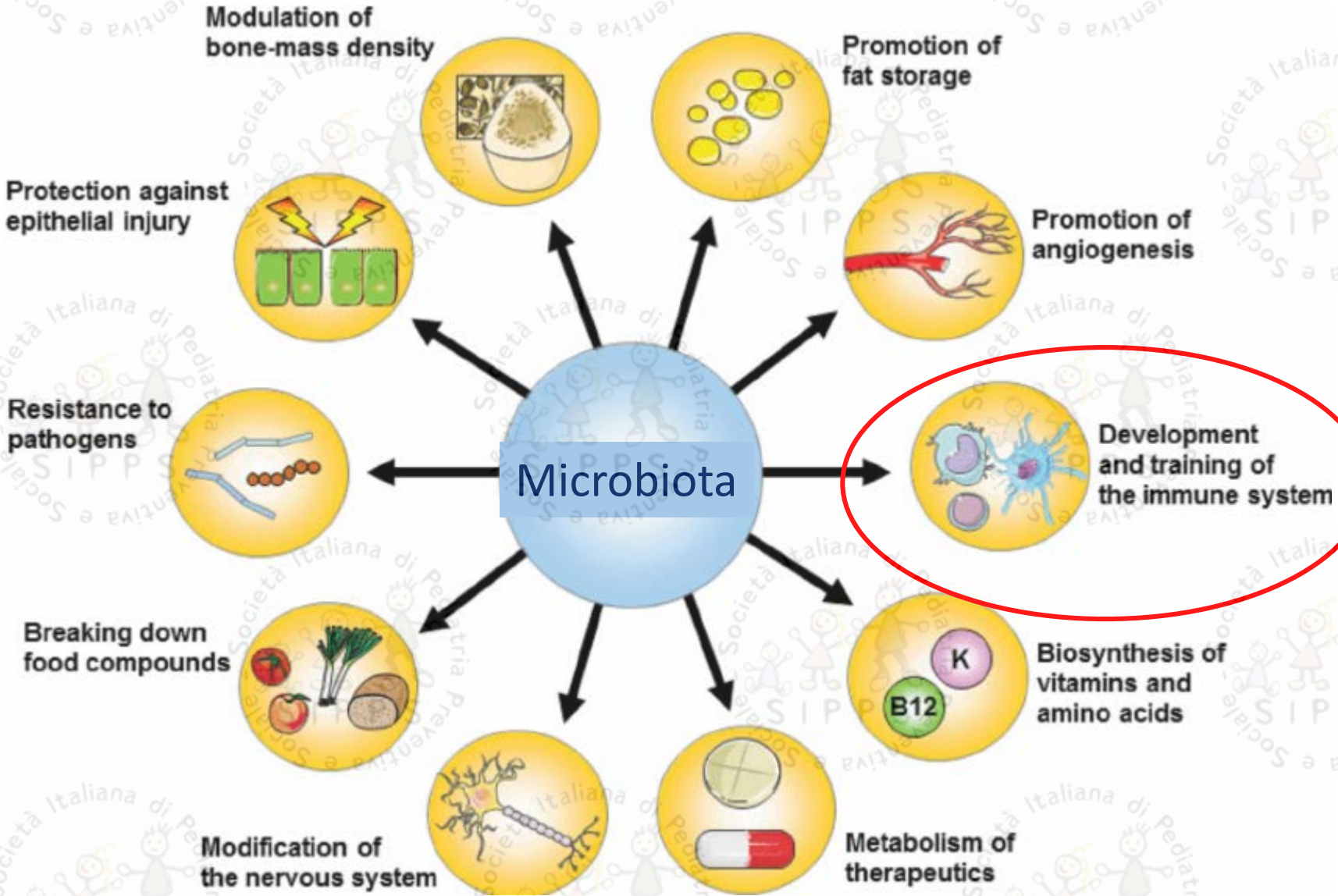
(Renz et al., J Allergy Clin Immunol 2017;140:24-40)

The microbiota of allergic diseases

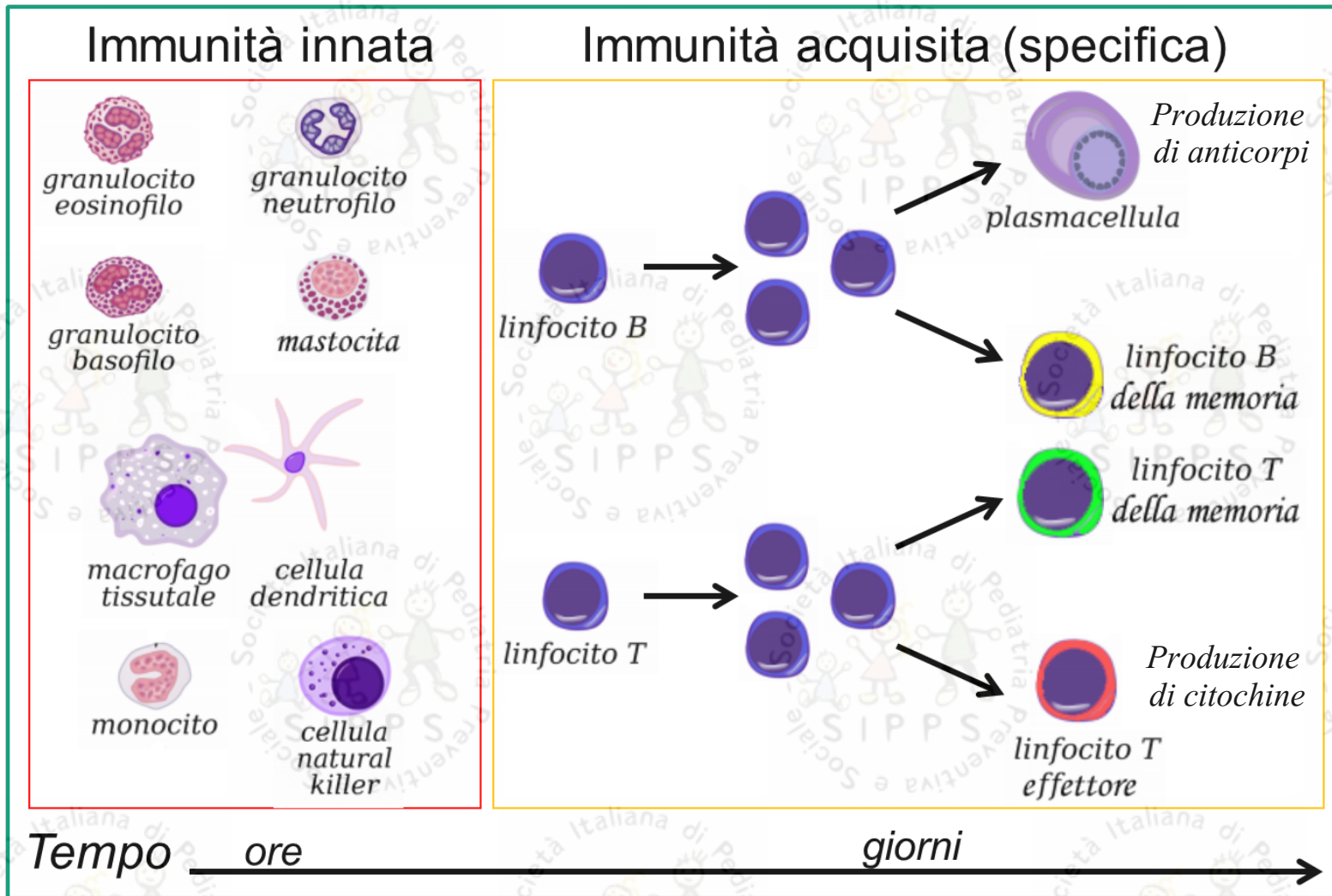


Environmental exposures alter bacterial diversity and increase inflammation. The result is tissue and gut dysbiosis with decreased bacterial diversity and changes in the microbiome of target organs. The alterations in normal flora likely interact with increased inflammation to alter patient phenotypes, such as disease response.

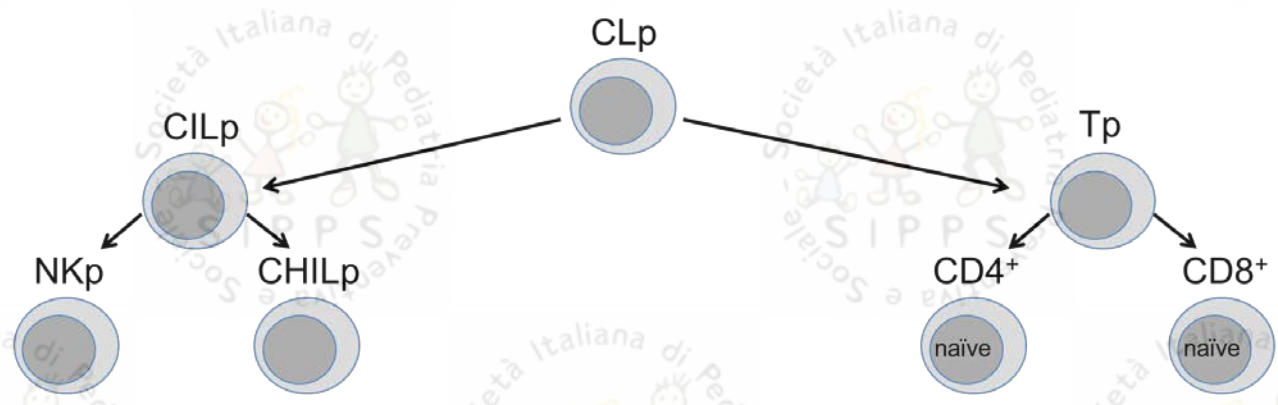
In che maniera il microbiota influenza la risposta immunitaria ?



Organizzazione della risposta immunitaria



The 3 major types of innate and adaptive cell-mediated effector immunity



Organizzazione della risposta immunitaria

Physical Triggers of Immune Response:

- **Infections**
 - Bacterial, viral
 - Fungal, parasitic
- **Toxins**
 - Exogenous
 - Endogenous
- **Food peptides**
- **Allergens**
- **Medications**
- **Auto antigens**

- Th17**
- Extracellular bacteria (skin, lining of intestine)
 - Fungi
 - Autoimmunity

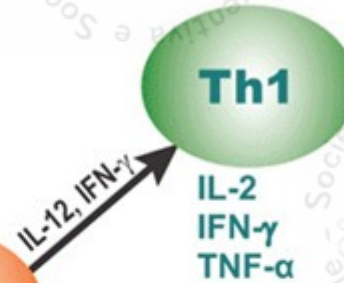


Antigen Presenting Cells



Naive T cell

Th0



- Th1**
- Cell-mediated immunity and inflammation
 - Intracellular pathogens
 - Viruses, bacteria
 - Autoimmunity
 - Inflammation



TGF-β
IL-35
IL-10

Treg

- Treg**
- Immune tolerance
 - Lymphocyte homeostasis
 - Regulation of immune responses

IL-4
IL-5
IL-6
IL-10
IL-13

Th2

- Th2**
- Antibody-mediated immunity
 - Extracellular parasites
 - Asthma, allergy

Th0: Naïve T cells

Th: Helper T cells

Treg: Regulatory T cells

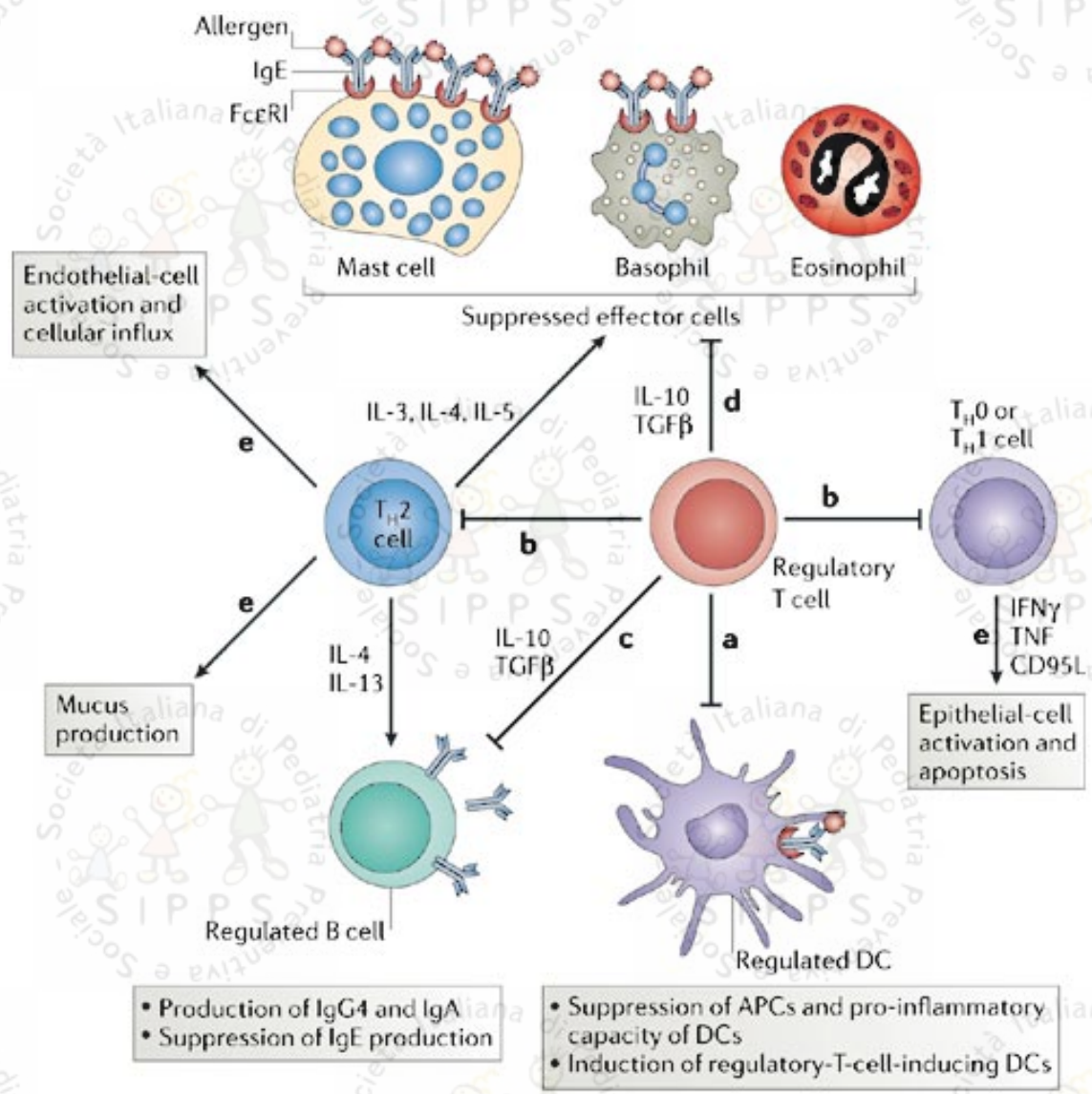
IL: Interleukin

TNF-α: Tumor necrosis factor-alpha

IFN-γ: Interferon-gamma

TGF-β: Transforming growth factor-beta

T-reg in the pathogenesis of allergic diseases

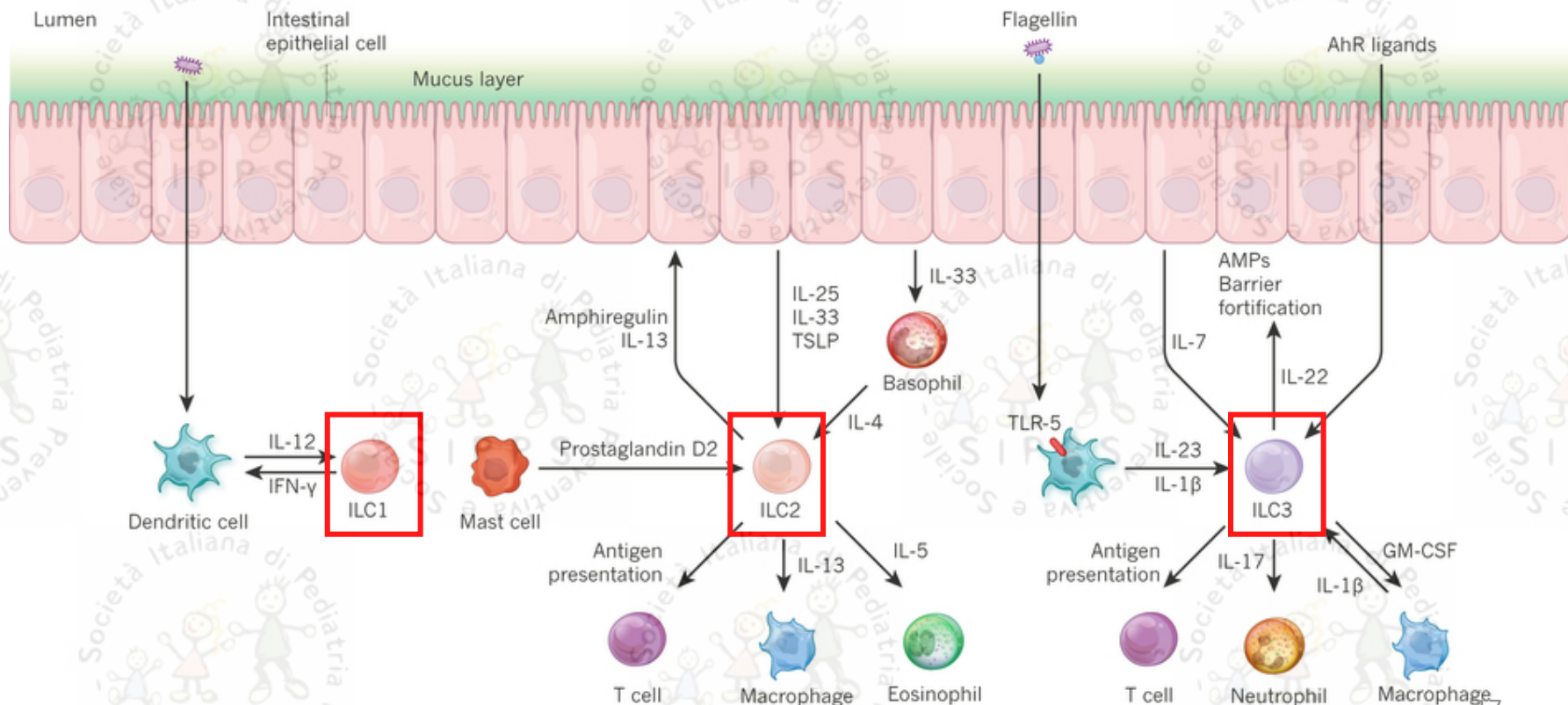


REVIEW

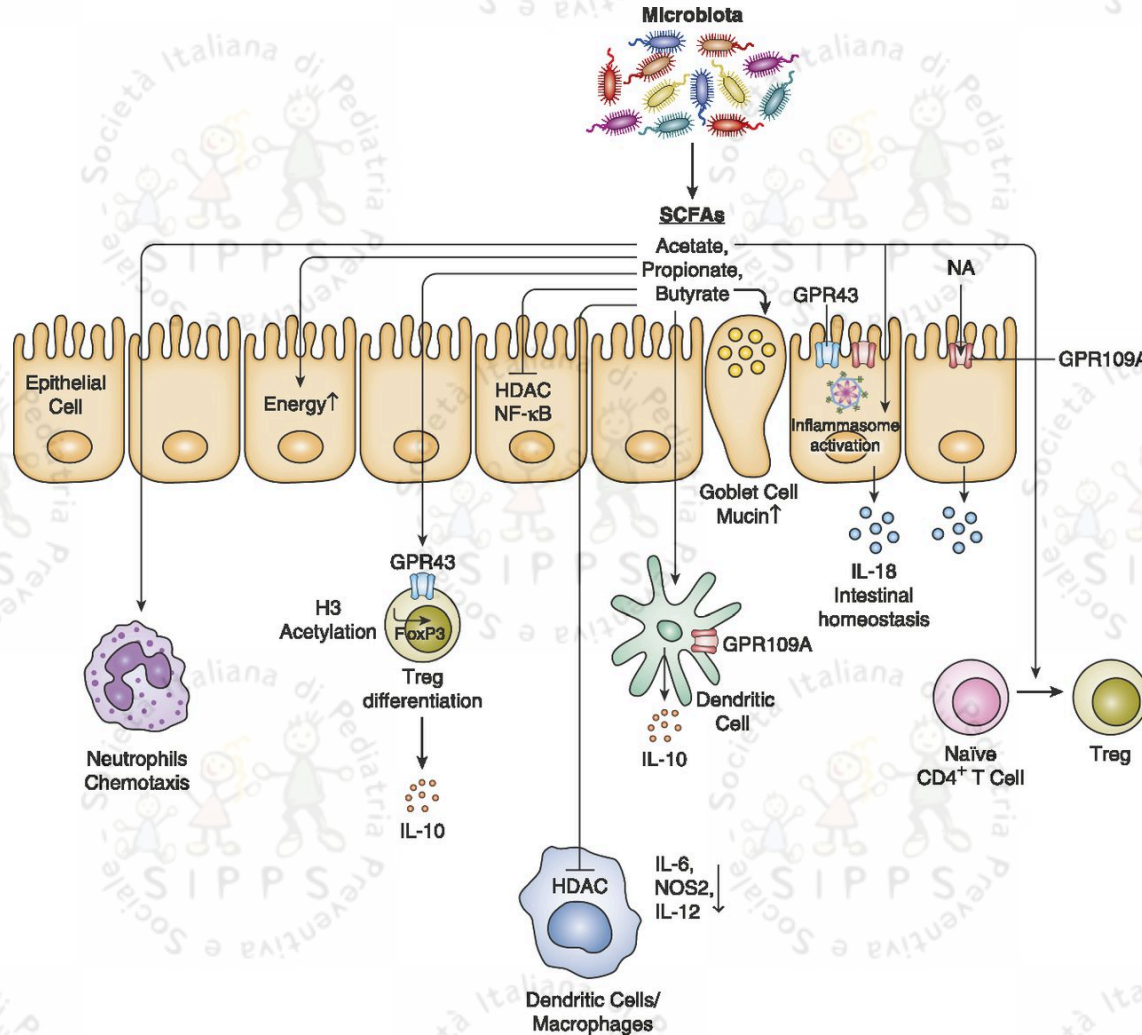
doi:10.1038/nature18847

The microbiome and innate immunity

Christoph A. Thaiss^{1*}, Niv Zmora^{1,2,3*}, Maayan Levy^{1*} & Eran Elinav¹

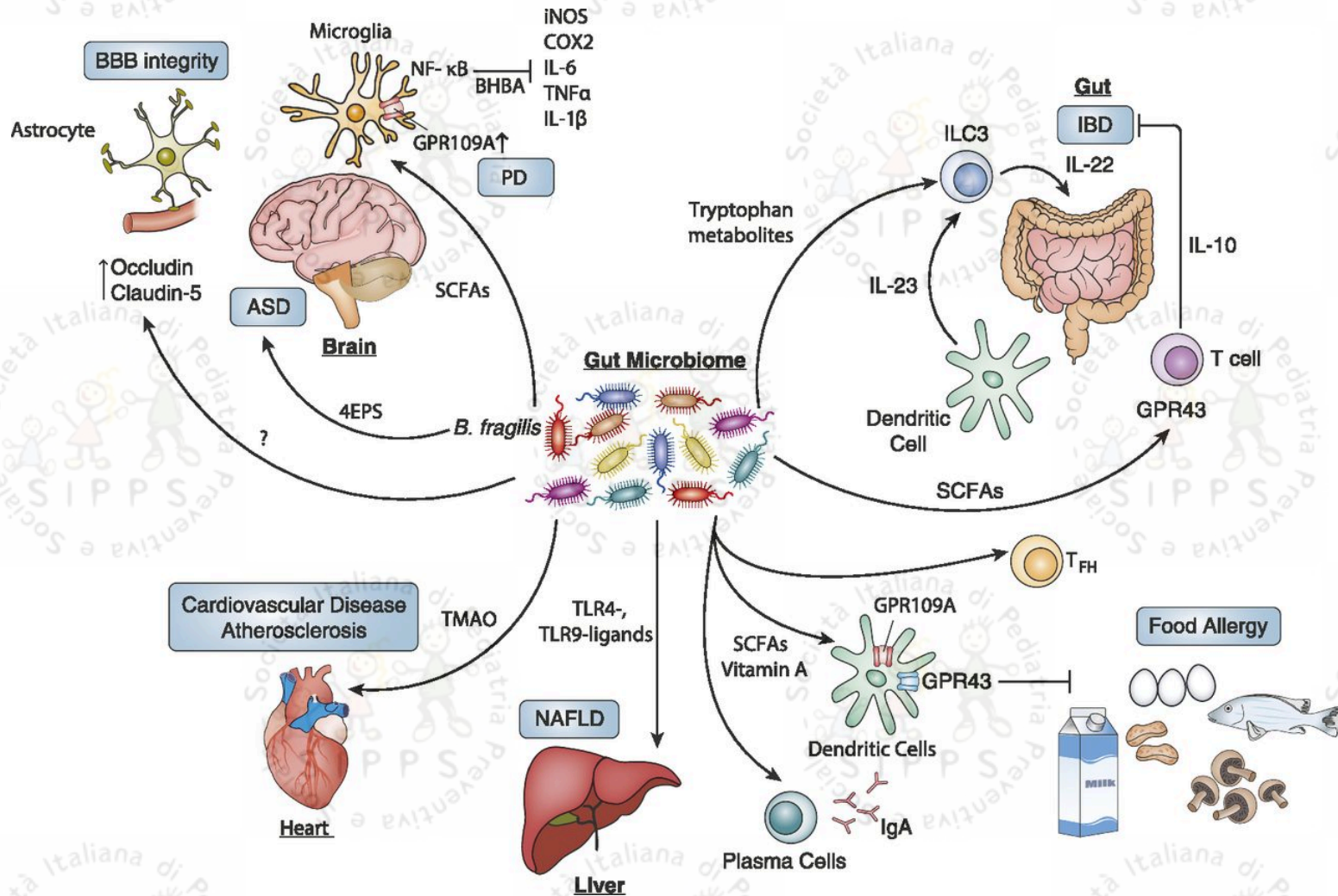


Microbiota-associated metabolites shape mucosal immunity.



Eran Blacher et al. *J Immunol* 2017;198:572-580

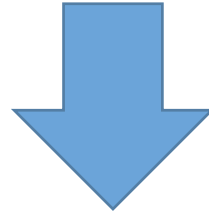
Microbiome-modulated metabolites and disease.



Eran Blacher et al. J Immunol 2017;198:572-580

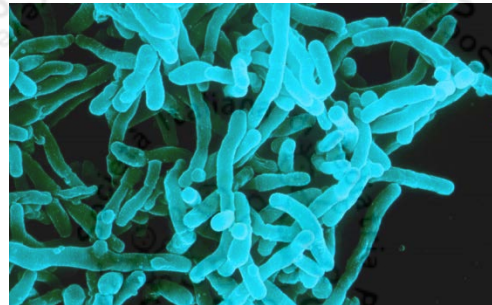
Si può modificare la risposta immunologica con i probiotici ?!

STRATEGIES TO MANIPULATE THE MICROBIOME



...appropriate microbiota manipulation (eg, with probiotics) can provide the most effective preventive and therapeutic effects and form part of a precision medicine approach.....

(J Allergy Clin Immunol 2017;139:1099-110.)

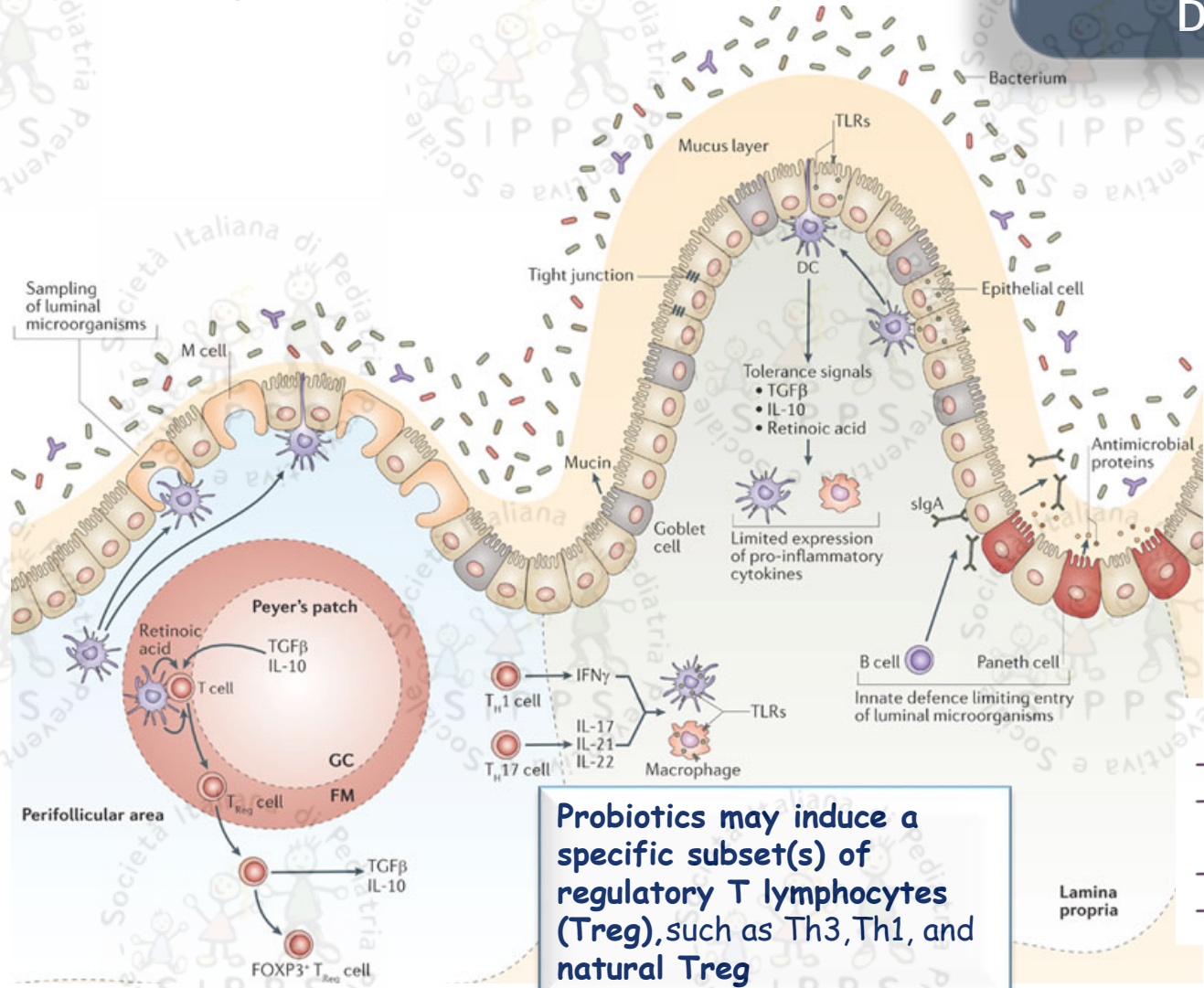


Emerging molecular insights into the interaction between probiotics and the host intestinal mucosa

Peter A. Bron^{1,2,3*}, Peter van Baarlen^{4*} and Michiel Kleerebezem^{1,2,5}

Abstract | Probiotic bacteria can modulate immune responses in the host gastrointestinal tract to promote health. The genomics era has provided novel opportunities for the discovery

RAZIONALE IMMUNOLOGICO PER L'IMPIEGO DEI PROBIOTICI NELLA PREVENZIONE DELLE MALATTIE ALLERGICHE E DELLE INFEZIONI



- Probiotics :**
- promoting gut barrier integrity
 - suppressing intestinal inflammatory response
 - inducing IgA production
 - tolerogenic immune responses

Lumen

Probiotics

Lactobacillus spp. and *Bifidobacterium* spp.

Intestinal epithelial cell

↓ Gut permeability

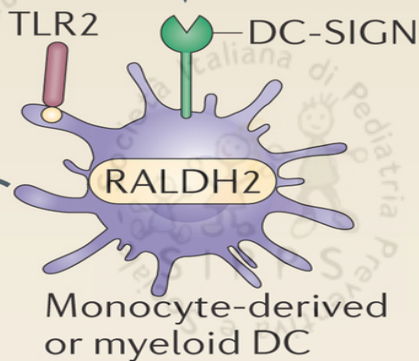
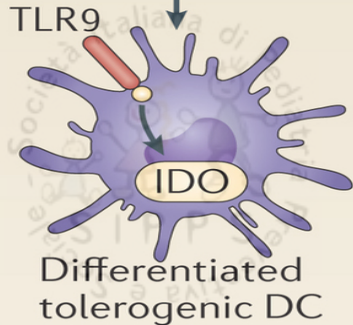
TLR2

RAZIONALE IMMUNOLOGICO PER L'IMPIEGO DEI PROBIOTICI NELLA PREVENZIONE DELLE MALATTIE ALLERGICHE

The activation of **TLR2** on intestinal epithelial cells decreases gut permeability

The activation of **TLR2** on myeloid dendritic cells (DCs) induces their differentiation into tolerogenic DCs and promotes the development of regulatory T (T_{Reg}) cells

The activation of **TLR9** on differentiated tolerogenic DCs which contributes to T_{Reg} cell development



RA



- ↑ Oral tolerance?
- ↓ Food allergy?
- Protection against asthma and atopic dermatitis?

Nature Reviews Immunology 15, 308–322 (2015)

Nature Reviews | Immunology

Identikit dei probiotici

Digestive and Liver Disease 49 (2017) 1177–1184

Contents lists available at ScienceDirect

 **ELSEVIER**

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld



Review Article

A consumer's guide for probiotics: 10 golden rules for a correct use

Marco Toscano^a, Roberta De Grandi^a, Luca Pastorelli^{b,c}, Maurizio Vecchi^{b,c}, Lorenzo Drago^{a,d,*}

^a Laboratory of Clinical Microbiology, Department of Biomedical Science for Health, University of Milan, Milan, Italy
^b Department of Biomedical Science for Health, University of Milan, Milan, Italy
^c Gastroenterology and Gastrointestinal Endoscopy Unit, IRCCS Policlinico San Donato, San Donato Milanese, Italy
^d Laboratory of Clinical-Chemistry and Microbiology, IRCCS Galeazzi Institute, University of Milan, Milan, Italy

 CrossMark



NON TUTTI I PROBIOTICI SONO UGUALI

Lisati microbici, batteri non vivi e spore non colonizzanti non sono considerati probiotici

VERO



FALSO

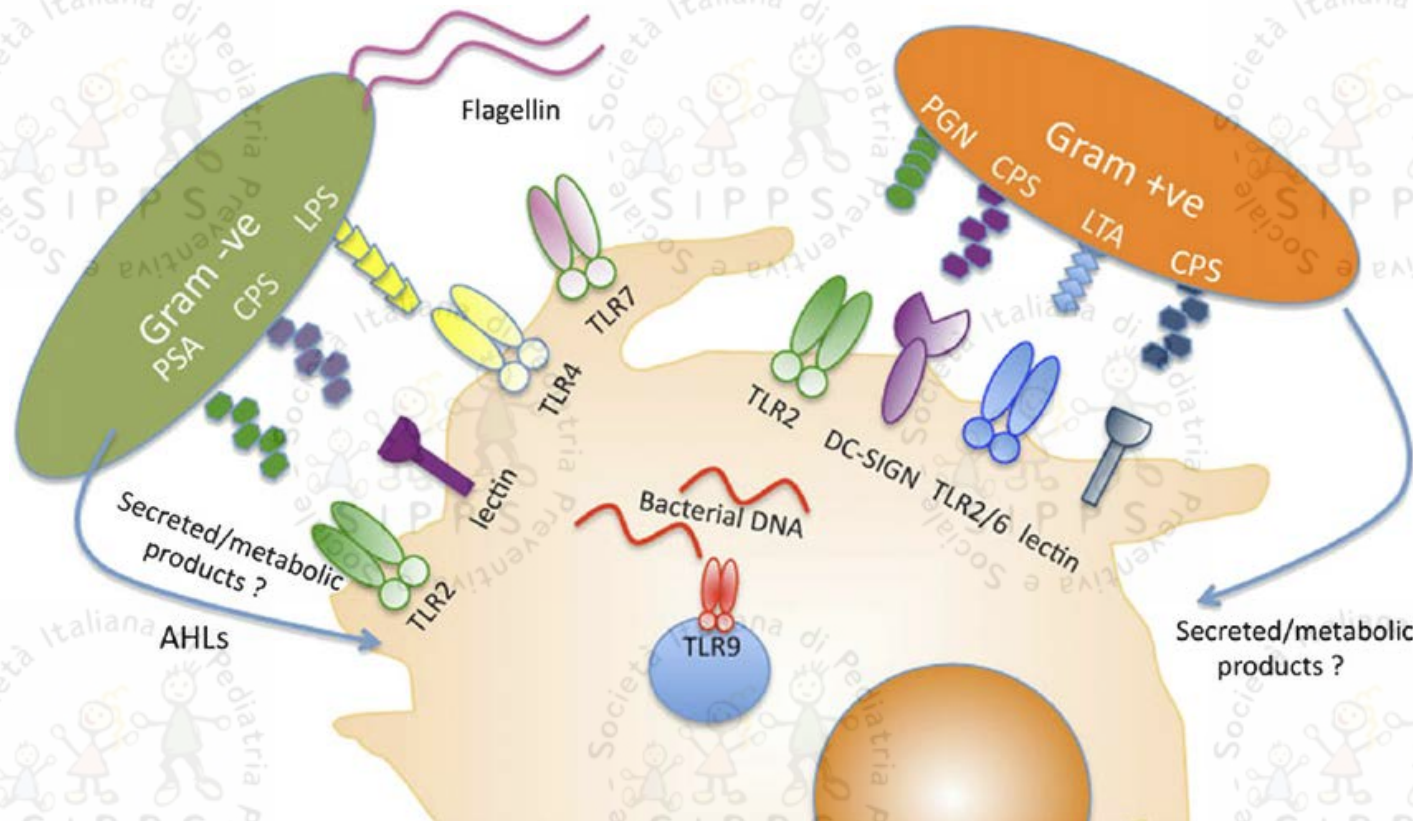


N.B. prodotti presenti sul mercato italiano > 1000

L' effetto del probiotico è ceppo specifico

I PROBIOTICI INCREMENTANO LA DIFFERENZIAZIONE DEI T-reg

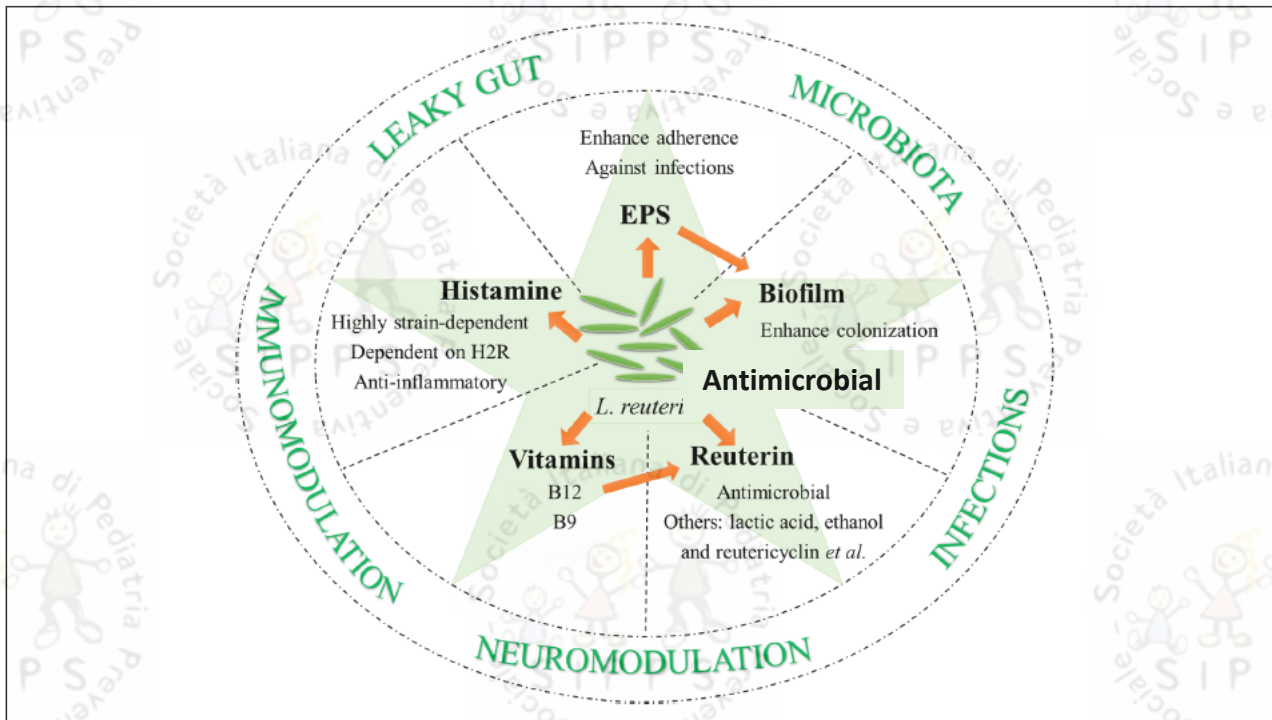
Lactobacillus spp. were found to bind toll-like receptors (TLRs) 2, 4, and 9 that prime monocyte-derived DCs to become tolerogenic and drive the development of Treg, which produce increased levels of IL-10



Role of *Lactobacillus reuteri* in Human Health and Diseases

Qinghui Mu, Vincent J. Tavella and Xin M. Luo*

There are multiple *L. reuteri* strains with different host origins, and many of the probiotic functions of *L. reuteri* are strain-dependent



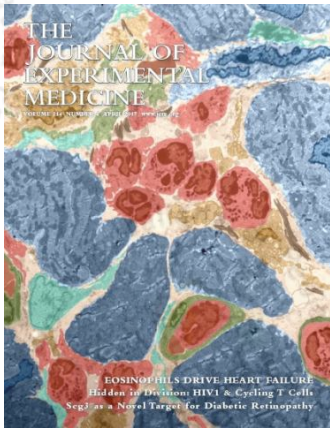
Lactobacillus reuteri exhibits strain-specific beneficial properties relevant to human health *L. reuteri* was first isolated in 1962



**Lactobacillus reuteri isolates derived
from four hosts. The genealogy of 119
L. reuteri strains**

L'effetto del probiotico è ceppo specifico

I PROBIOTICI POSSONO RIMODELLARE IL MICROBIOTA E LA RISPOSTA IMMUNITARIA



Published December 19, 2016

JEM

Article

Resetting microbiota by *Lactobacillus reuteri* inhibits
T reg deficiency–induced autoimmunity via adenosine
A_{2A} receptors

Baokun He,^{1,2} Thomas K. Hoang,^{1,2} Ting Wang,^{1,2} Michael Ferris,⁵ Christopher M. Taylor,⁵
Xiangjun Tian,⁶ Meng Luo,⁵ Dat Q. Tran,² Jain Zhou,³ Nina Tatevian,³ Fayong Luo,⁴ Jose G. Molina,⁴
Michael R. Blackburn,⁴ Thomas H. Gomez,⁷ Stefan Roos,^{8,9} J. Marc Rhoads,^{1,2} and Yuying Liu^{1,2}

J. Exp. Med. 2017 Vol. 214 No. 1 107–12

Lactobacillus reuteri DSM 17938 treatment
reprograms gut microbiota in T reg cell
deficiency

Remodeling microbiota with *Lactobacillus reuteri* prolonged survival and reduced multiorgan inflammation in T reg deficient SF mice

Treg deficient scurfy mouse

WITHOUT *L. reuteri* treatment



Gut microbial dysbiosis

Autoimmunity

(T_H1/T_H2 Cells \uparrow ; Cytokines
IFN- γ and IL-4 \uparrow)



Multi-organ Inflammation

Early death

Treg deficient scurfy mouse

WITH *L. reuteri* treatment



Remodeled gut microbiota



\uparrow Inosine



A_{2A} receptor



T effector cells (T_H1/T_H2)



\downarrow T_H1/T_H2 differentiation

\downarrow Cytokines IFN- γ and IL-4



\downarrow Multi-organ inflammation

\uparrow Survival

L' effetto del probiotico è ceppo specifico

L. Reuteri remodels gut microbiota, alters the metabolites, and protects against T reg cell deficiency-induced autoimmunity by suppressing Th1/Th2 cells via inosine-adenosine A_{2A} interaction

May 3

BREAKING NEWS

JCI insight

JCI Insight. 2018;3(9)

RESEARCH ARTICLE

First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis

Ian A. Myles,¹ Noah J. Earland,¹ Erik D. Anderson,¹ Ian N. Moore,² Mark D. Kieh,¹ Kelli W. Williams,¹ Arhum Saleem,¹ Natalia M. Fontecilla,¹ Pamela A. Welch,¹ Dirk A. Darnell,¹ Lisa A. Barnhart,¹ Ashleigh A. Sun,¹ Gulbu Uzel,¹ and Sandip K. Datta¹

10 adult and 5 pediatric patients were enrolled in an open-label phase I/II safety and activity trial

Treatment with *R. mucosa* was associated with significant decreases in measures of disease severity, topical steroid requirement, and *S. aureus* burden. There were no adverse events or treatment complications.



JCI Insight. 2018;3(9)

Figure 2. Topical *Roseomonas mucosa* shows activity against atopic dermatitis in adults.

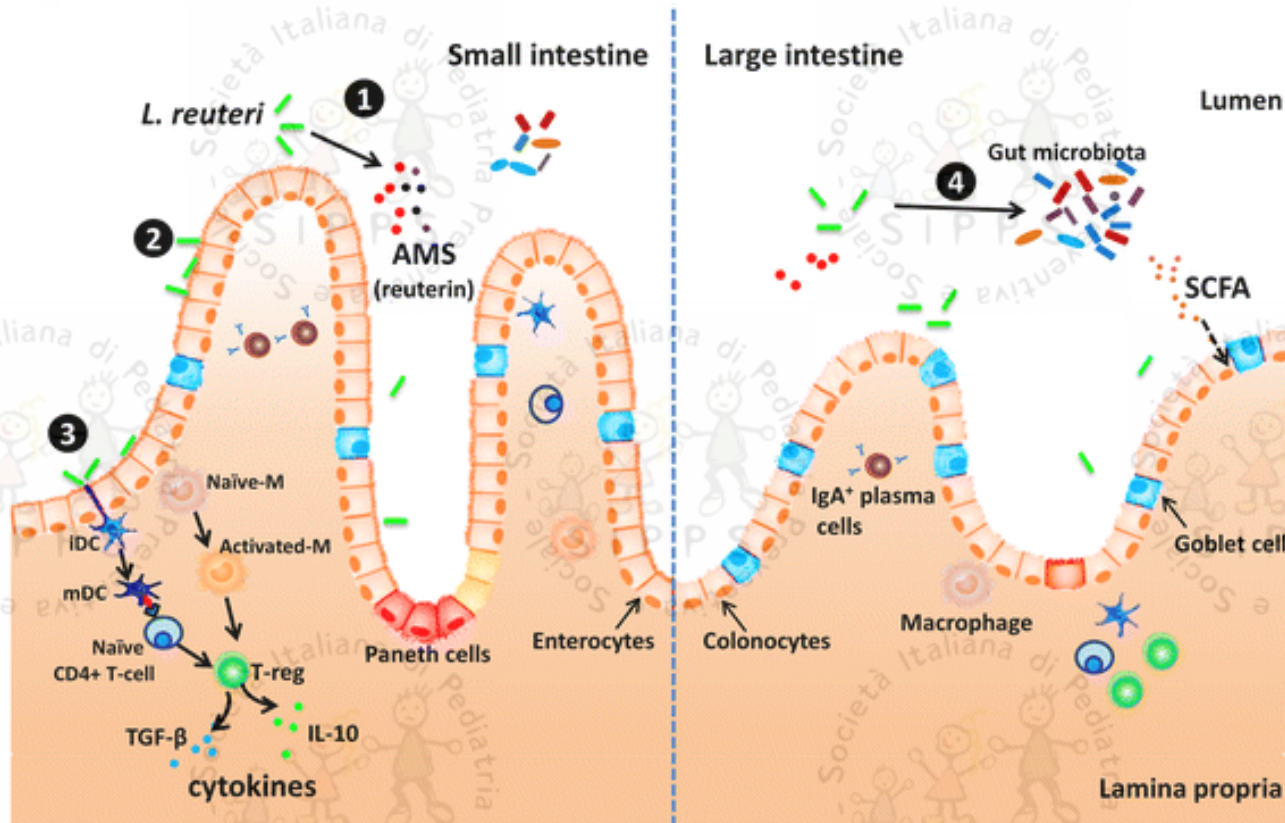


Figure 3. Topical *Roseomonas mucosa* shows activity against atopic dermatitis in children.

Roseomonas mucosa, presenta delle differenze nei profili metabolici a seconda che sia raccolto dalla cute di soggetti sani o di pazienti con dermatite atopica.

L'analisi dei metaboliti di *R. mucosa*, infatti, ha dimostrato che, nei pazienti, venivano prodotti monometilglutarato e istidina (azione irritativa) mentre nei sani prevalevano fosfadilcolina e fosfadilietanolamina-ceramide (funzione barriera e immunomodulatoria).

LACTOBACILLUS REUTERI DSM 17938 E PRODUZIONE DI REUTERINA E IgA ; INDUCE UNA RISPOSTA T-REG



Journal of Animal Science and Biotechnology December 2015, 6:14

L. reuteri also competes for receptors and binding sites with other intestinal microbes on the intestinal mucosa

Scegliere probiotici che resistono all'ambiente gastrointestinale

I probiotici orali dovrebbero essere resistenti all'ambiente acido gastrico e alla bile per esercitare i loro effetti benefici e dovrebbero avere una buona qualità microbiologica per risultare sicuri per il consumo umano.

Toscano M, et al. A consumer's guide for probiotics: 10 golden rules for a correct use. *Dig Liver Dis.* 2017



**Multiple *L. reuteri* strains are resistant to low pH and bile salts .
This resistance is believed to be at least partially dependent on its
ability to form biofilms**

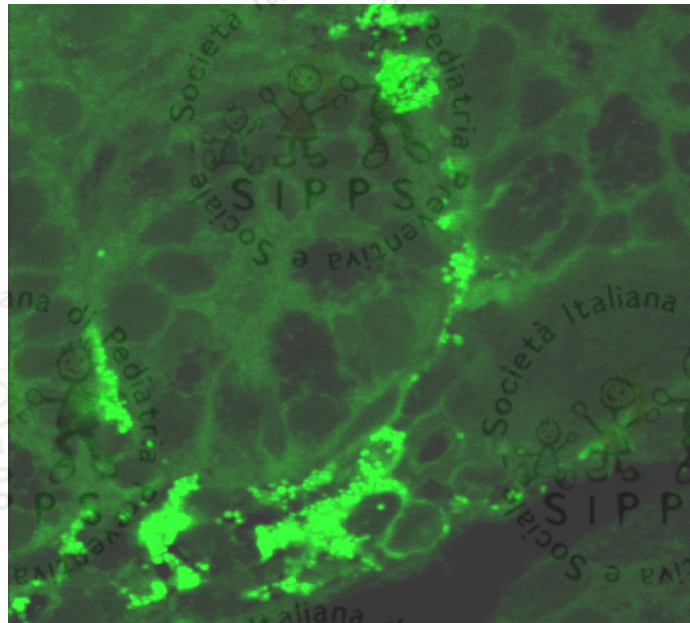
Frontiers in Microbiology | www.frontiersin.org 10 April

2018 | Volume 9 | Article 757

Probiotici e colonizzazione intestinale

Scegliere probiotici che interagiscono positivamente con il microbiota intestinale

L. Reuteri modula le funzioni immunitarie a livello intestinale



Numerous studies have demonstrated that biofilm formation by **L. REUTERI DSM 17938** is a beneficial property because it promotes colonization and a longer permanence of LAB in the mucosa of the host.

Research article

Open Access

Probiotic *Lactobacillus reuteri* biofilms produce antimicrobial and anti-inflammatory factors

Sara E Jones^{1,3} and James Versalovic^{*2,3}

Address: ¹Cell and Molecular Biology Program, Baylor College of Medicine, Houston, Texas 77030, USA, ²Department of Pathology, Baylor College of Medicine, Houston, Texas 77030, USA and ³Department of Pathology, Texas Children's Hospital, Houston, Texas 77030, USA

Email: Sara E Jones - saraj@bcm.edu; James Versalovic* - jamesv@bcm.edu

* Corresponding author

- **Lactobacillus reuteri** formed biofilms that retained functions potentially advantageous to the host including modulation of cytokine output and the production of the antimicrobial agent, **reuterin**.
- **L. reuteri** biofilms differed in the **quantities of reuterin secreted in this physiological state**.
- Reuterin can inhibit a wide range of microorganisms, mainly Gram-negative bacteria
- Not surprisingly, most *Lactobacillus* species are resistant to reuterin, among which *L. reuteri* strains exert the most resistance

Probiotici per la prevenzione ed il trattamento delle infezioni respiratorie

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

STUDIO RANDOMIZZATO IN DOPPIO CIECO CONTRO PLACEBO
CON *LACTOBACILLUS REUTERI* (17938) AL FINE DI VERIFICARE L' EFFETTO
PREVENTIVO SULLE INFEZIONI INTESTINALI E RESPIRATORIE

PEDIATRICS 133,4,2014



12 settimane di trattamento attivo
(prima dell' inizio dell' anno scolastico)
e 12-24 di Follow-up



L reuteri was better than placebo in reducing :

- number of doctor visits,
- antibiotic use,
- absenteeism from day school and parental absenteeism from work

A cost-benefit analysis revealed significant reductions in costs in the *L reuteri*-treated children.

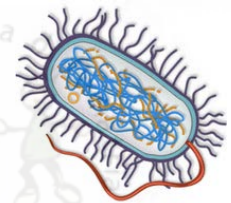
- No adverse events related to the study product were reported.

Probiotici: *evidenze?*

Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea A Systematic Review and Meta-analysis

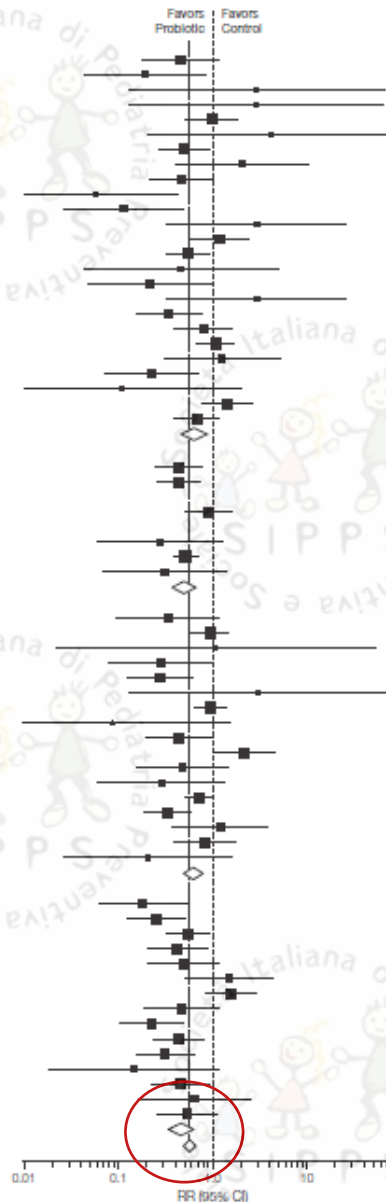
JAMA. 2012;307(18):1959-1969

RCT
11811 patients



No. With Antibiotic-Associated Diarrhea/No. in Group (%)

Study	No. With Antibiotic-Associated Diarrhea/No. in Group (%)		RR (95% CI)
	Intervention	Control	
Genus, Bifidobacterium			
Genus, Bifidobacterium			
Imphiyil ²⁰ 2002	3/5 (38)	8/10 (80)	0.47 (0.18-1.21)
Shou ²¹ 2002	2/60 (2)	10/80 (12)	0.20 (0.05-0.88)
Sullivan ²² 2003	1/12 (8)	0/12 (0)	3.00 (0.13-66.80)
Lighthouse ²³ 2004	1/10 (10)	0/10 (0)	3.00 (0.14-65.55)
Plummer ²⁴ 2004	15/69 (22)	15/69 (22)	1.00 (0.53-1.88)
Schrotenmaier ²⁵ 2004	2/50 (4)	0/43 (0)	4.31 (0.21-87.30)
Comba ¹⁶ 2005	13/67 (19)	24/82 (29)	0.51 (0.28-0.93)
Myllyluoma ²¹ 2005	4/23 (17)	2/24 (8)	2.09 (0.42-10.32)
Conway ²⁴ 2007	9/149 (6)	17/137 (12)	0.49 (0.22-1.06)
de Bontol ²⁵ 2007	1/105 (1)	16/101 (16)	0.06 (0.01-0.44)
Park ²⁶ 2007	2/176 (1)	17/176 (10)	0.12 (0.03-0.50)
Stohr ²⁴ 2007	3/21 (14)	1/21 (5)	3.00 (0.34-26.56)
Kim ²⁷ 2008	16/168 (10)	14/179 (8)	1.22 (0.61-2.42)
Koning ²⁸ 2008	9/20 (45)	17/21 (81)	0.56 (0.33-0.94)
Saymar ²⁸ 2008	1/40 (2)	1/43 (5)	0.48 (0.04-5.23)
Warius ²⁹ 2008	2/45 (4)	9/41 (22)	0.22 (0.05-0.99)
Engelbrektsen ³⁰ 2009	3/20 (15)	1/20 (5)	3.00 (0.34-26.45)
Hickox ¹⁹ 2007	7/59 (10)	19/66 (29)	0.35 (0.16-0.78)
Moranstein ²¹ 2009	11/61 (18)	14/64 (22)	0.82 (0.41-1.67)
Koning ³¹ 2010	13/17 (76)	9/13 (69)	1.10 (0.71-1.73)
de Vrese ³² 2011	4/50 (13)	3/29 (10)	1.29 (0.32-5.26)
Sanooyan ³³ 2011	3/25 (12)	13/25 (52)	0.23 (0.07-0.71)
Selinger ³⁴ 2011	0/62 (0)	4/62 (6)	0.11 (0.01-2.02)
Yoon ³⁵ 2011	20/151 (13)	17/186 (9)	1.45 (0.79-2.67)
Bhatti ³⁶ 2011	19/176 (11)	25/167 (15)	0.69 (0.40-1.20)
Random effects model			0.68 (0.49-0.88)
Genus, Bacillus			
Li 2010 ³⁷	15/122 (12)	34/125 (27)	0.45 (0.26-0.79)
La Rosa ⁴² 2003	14/60 (23)	31/60 (52)	0.45 (0.27-0.76)
Genus, Bifidobacterium			
Yazar ³⁸ 2010	14/38 (37)	15/38 (39)	0.93 (0.53-1.66)
Genus, Enterococcus			
Borgia ³⁹ 1982	2/40 (5)	7/40 (18)	0.29 (0.05-1.29)
Figuroa ⁴⁰ 1982	57/561 (10)	107/562 (19)	0.53 (0.39-0.72)
Wunderslich ⁴⁰ 1989	2/23 (9)	5/22 (27)	0.32 (0.07-1.41)
Random effects model			0.51 (0.38-0.68)
Genus, Lactobacillus			
Gotz ²² 1979	3/48 (6)	9/50 (18)	0.35 (0.10-1.21)
Tankowicz ⁴³ 1990	10/15 (67)	15/23 (70)	0.95 (0.61-1.50)
Reid ³⁴ 1992	0/19 (0)	0/21 (0)	1.10 (0.02-52.05)
Arvola ²⁷ 1999	3/69 (3)	9/78 (12)	0.29 (0.08-1.04)
Vandorhoof ²⁷ 1999	7/69 (8)	25/96 (26)	0.29 (0.13-0.63)
Felley ³⁴ 2001	1/26 (4)	0/27 (0)	3.11 (0.13-73.07)
Thomas ³⁰ 2001	39/152 (26)	40/150 (27)	0.96 (0.66-1.41)
Turst ³² 2004	0/35 (0)	5/35 (14)	0.09 (0.01-1.58)
Beausoleil ¹⁷ 2004	7/44 (16)	16/45 (36)	0.45 (0.20-0.98)
Ruzanyanski ⁴⁴ 2008	20/120 (17)	9/120 (8)	2.22 (1.06-4.68)
Saldar ⁴⁵ 2008	4/23 (17)	6/17 (36)	0.49 (0.16-1.48)
Szajewicka ⁴⁶ 2009	2/44 (5)	5/39 (13)	0.30 (0.06-1.38)
Sampalis ⁴⁷ 2010	47/233 (20)	65/239 (27)	0.74 (0.53-1.03)
Gao ⁴⁸ 2010	13/85 (15)	37/84 (44)	0.34 (0.20-0.53)
Lönnemark ⁴⁴ 2010	6/116 (5)	5/121 (4)	1.29 (0.39-3.92)
Song ⁴⁹ 2010	11/103 (11)	14/111 (13)	0.85 (0.40-1.79)
Crippenman ⁵⁰ 2011	1/15 (7)	5/16 (31)	0.21 (0.03-1.52)
Random effects model			0.64 (0.47-0.88)
Genus, Saccharomyces			
Ligny ⁵² 1975	3/20 (15)	16/20 (80)	0.19 (0.06-0.54)
Adam ²⁶ 1977	9/199 (5)	33/189 (17)	0.26 (0.13-0.53)
Monteiro ⁵³ 1981	19/121 (16)	33/119 (28)	0.57 (0.34-0.94)
Surawicz ²⁴ 1989	11/116 (9)	14/64 (22)	0.43 (0.21-0.90)
McFarland ³² 1995	7/67 (7)	14/95 (15)	0.49 (0.21-1.17)
Lowt ²⁴ 1998	7/53 (13)	5/35 (14)	1.53 (0.54-4.35)
Berthamou ⁵⁴ 1999	25/388 (6)	15/391 (4)	1.57 (0.85-2.90)
Erdove ⁵⁵ 2004	7/127 (6)	12/105 (11)	0.48 (0.20-1.18)
Erdove ⁵⁵ 2004	7/117 (6)	30/117 (26)	0.23 (0.11-0.51)
Duman ⁵⁶ 2005	14/204 (7)	28/185 (15)	0.45 (0.25-0.83)
Kotowska ⁵⁷ 2005	9/132 (7)	29/137 (21)	0.32 (0.16-0.65)
Chan ⁵⁸ 2005	3/11 (3)	7/78 (9)	0.15 (0.02-1.21)
Cindonak ²⁹ 2007	0/52 (0)	19/62 (31)	0.47 (0.23-0.95)
Bravo ²⁷ 2008	3/41 (7)	5/45 (11)	0.65 (0.17-2.58)
Song ³⁴ 2010	11/330 (3)	20/331 (6)	0.55 (0.27-1.13)
Random effects model			0.48 (0.35-0.66)
Overall random effects model			0.58 (0.50-0.68)



RR (95% CI)

Probiotici per la prevenzione ed il trattamento delle infezioni respiratorie



**Cochrane
Library**

Cochrane Database of Systematic Reviews

PROBIOTICS FOR PREVENTING ACUTE UPPER RESPIRATORY TRACT INFECTIONS (REVIEW)

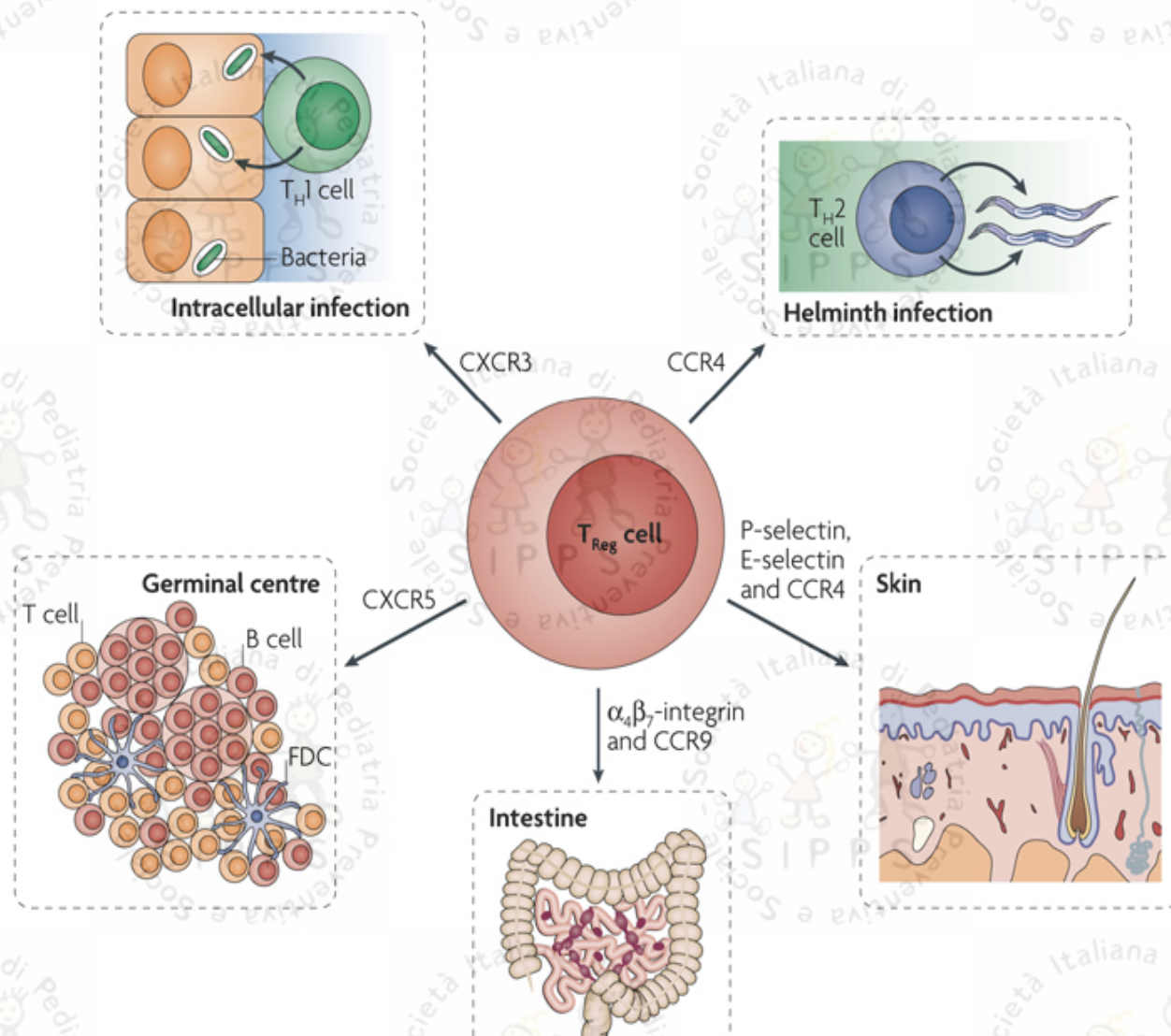
AUTHORS' CONCLUSIONS:

Probiotics were better than placebo in

1. **reducing the number** of participants experiencing **episodes of acute URTI**
2. **mean duration of an episode of acute URTI,**
3. **antibiotic use**
4. **cold-related school absence.**

This indicates that probiotics may be more beneficial than placebo for preventing acute URTIs.

I probiotici inducono una risposta T-REG



Ruolo dei linfociti T-Reg nella difesa nei confronti degli agenti infettivi



Crying Time and ROR γ /FOXP3 Expression in *Lactobacillus reuteri* DSM17938-Treated Infants with Colic: A Randomized Trial

Francesco Savino, MD, PhD¹, Maria Garro, MD¹, Paola Montanari, BS², Ilaria Galliano, PhD², and Massimiliano Bergallo, PhD²

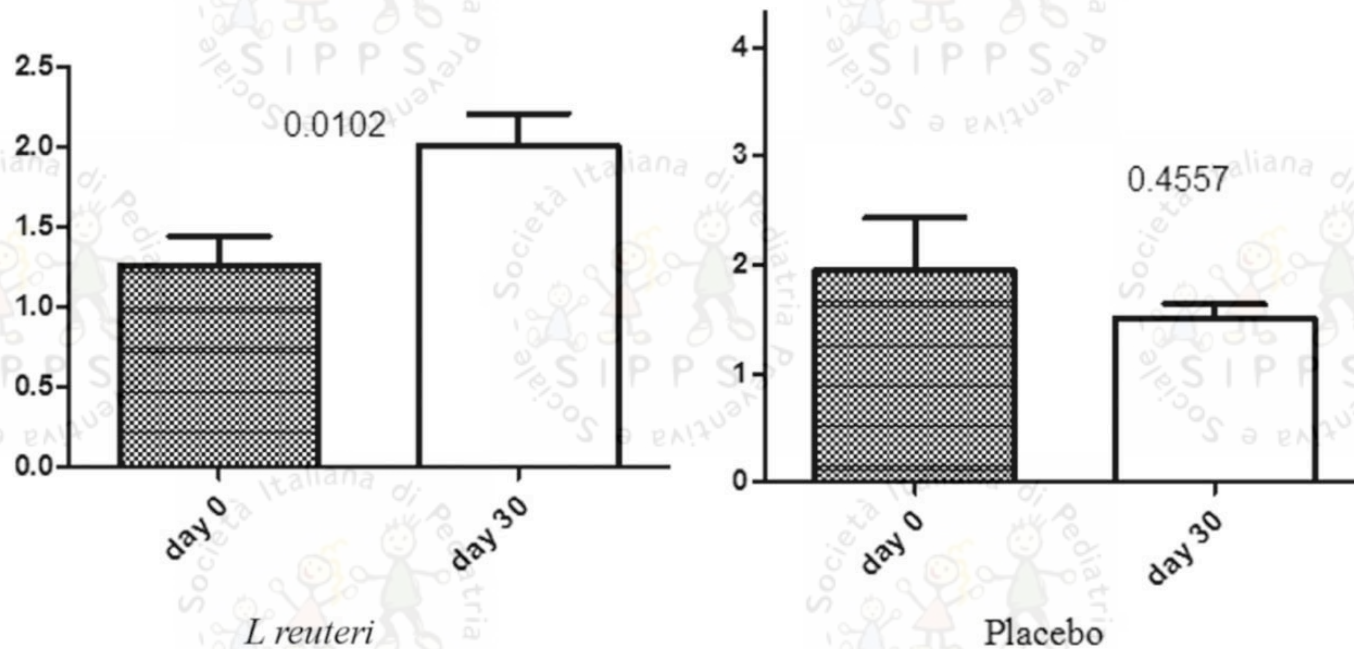
Conclusions : Infants with colic treated with *L reuteri* DSM 17938 for 30 days had a significantly decreased crying time and an increased FOXP3 concentration, resulting in a decreased ROR γ /FOXP3 ratio. **The treatment reduced fecal calprotectin. (J Pediatr 2018;192:171-7).**

The treatment included 5 drops of *Lreuteri*DSM 17938 (1×10^8 colony-forming units per drop) in an oil suspension for 1 month.



Crying Time and ROR γ /FOXP3 Expression in *Lactobacillus reuteri* DSM17938-Treated Infants with Colic: A Randomized Trial

Francesco Savino, MD, PhD¹, Maria Garro, MD¹, Paola Montanari, BS², Ilaria Galliano, PhD², and Massimiliano Bergallo, PhD²



Expression of FoxP3(T-REG) at day 0 and day 30 in infants treated with *L reuteri* or placebo

Compared with the post-placebo results, it is likely that the probiotic induced both local and systemic reductions in inflammation.

Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis

Valerie Sung, PhD,^a Frank D'Amico, PhD,^{b,c} Michael D. Cabana, MD,^d Kim Chau, PhD,^e Gideon Koren, MD,^e Francesco Savino, PhD,^f Hania Szajewska, MD,^g Girish Deshpande, MSc,^h Christophe Dupont, PhD,ⁱ Flavia Indrio, MD,^j Silja Mentula, PhD,^k Anna Partty, PhD,^l Daniel Tancredi, PhD^m

Pediatrics.2018 Jan;141(1)

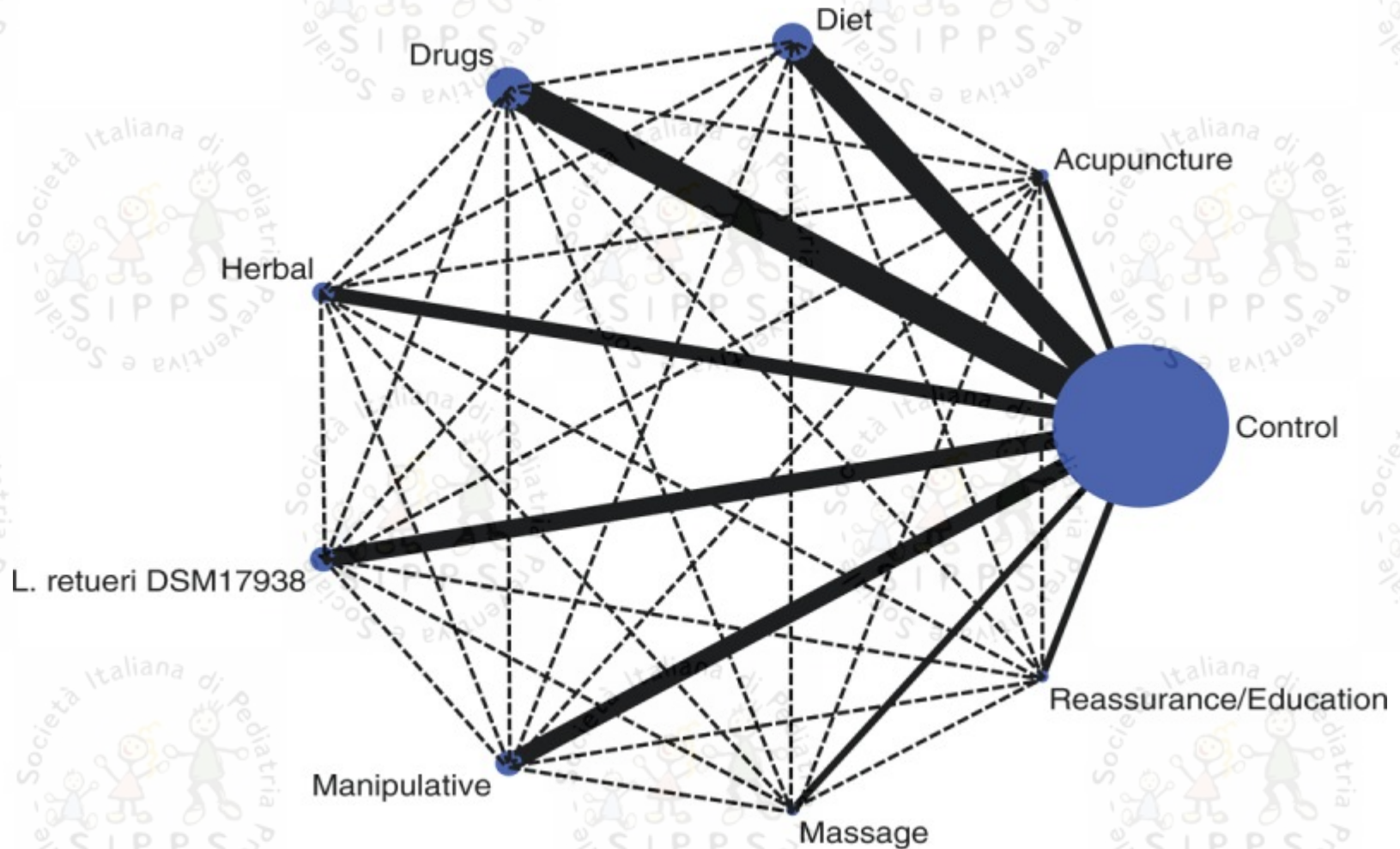
Infant colic is characterized by immoderate crying and affects 10–30% infants

It is acutely associated with maternal depression, long-term adverse effects on child behavior, sleep, and allergy outcomes

CONCLUSIONS: *L reuteri* DSM17938 is effective and can be recommended for breastfed infants with colic.

EFFICACY OF LACTOBACILLUS REUTERI DSM 17938 FOR INFANTILE COLIC: SYSTEMATIC REVIEW WITH NETWORK META-ANALYSIS.

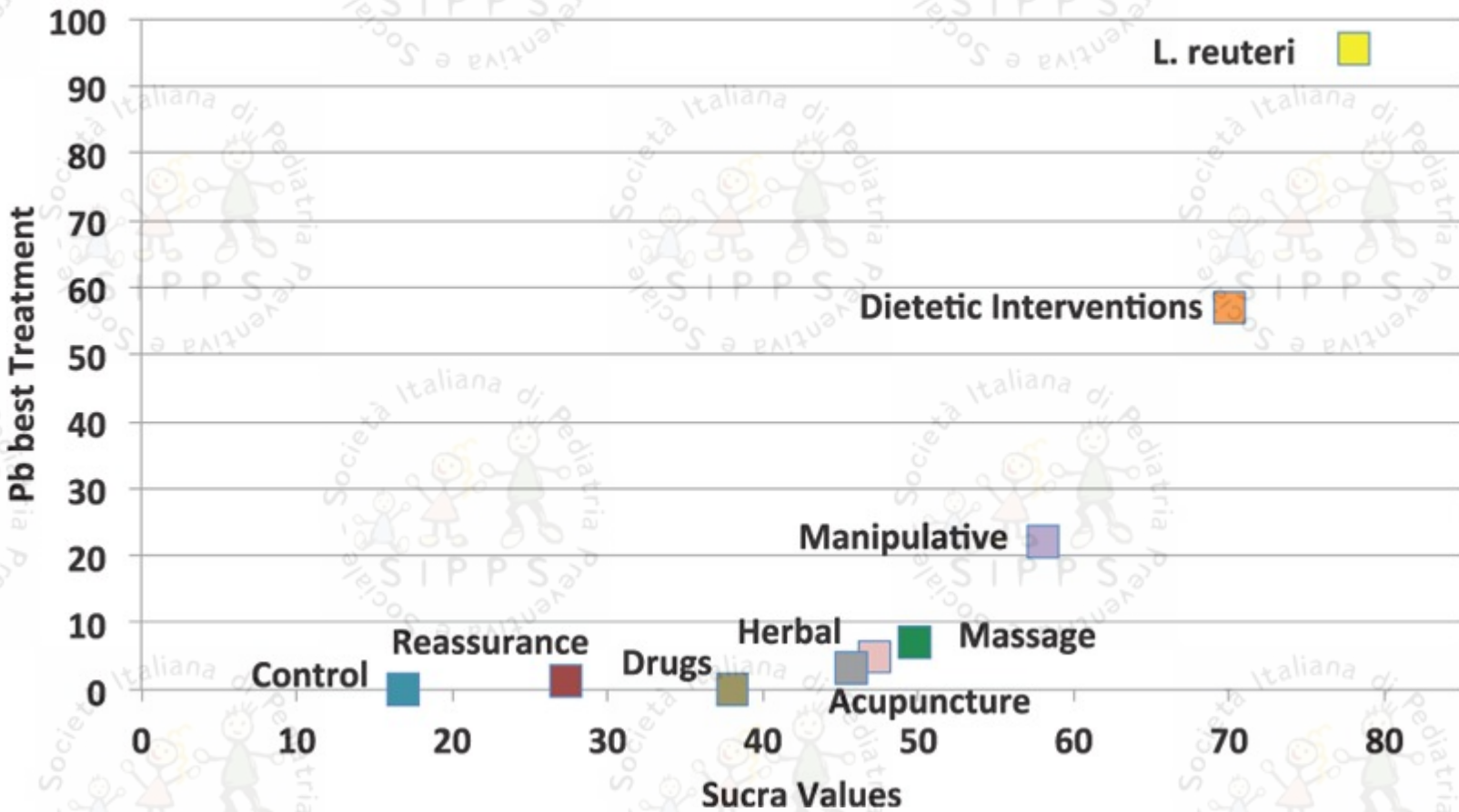
Medicine. 96(51):e9375, DEC 2017



EFFICACY OF LACTOBACILLUS REUTERI DSM 17938 FOR INFANTILE COLIC: SYSTEMATIC REVIEW WITH NETWORK META-ANALYSIS.

Medicine. 96(51):e9375, DEC 2017

Best Treatment Analysis



I PROBIOTICI PER "MODIFICARE" IL MICROBIOMA E LA "MARCIA ALLERGICA"

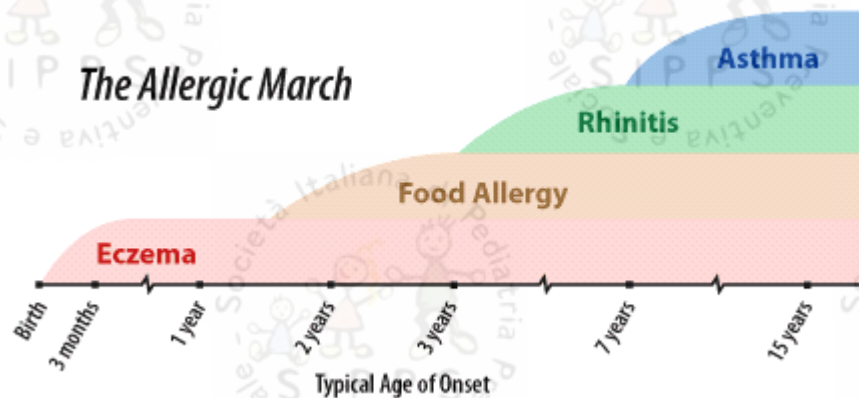
PRACTALL consensus report (J Allergy Clin Immunol 2017;139:1099-110.)

The microbiome in allergic disease: Current understanding and future opportunities—2017 PRACTALL document of the American Academy of Allergy, Asthma & Immunology and the European Academy of Allergy and Clinical Immunology



Yvonne J. Huang, MD,^a Benjamin J. Marsland, PhD,^b Supinda Bunyavanich, MD, MPH, MPhil,^c Liam O'Mahony, PhD,^d Donald Y. M. Leung, MD, PhD,^e Antonella Muraro, MD, PhD,^f and Thomas A. Fleisher, MD^g *Ann Arbor, Mich, Lausanne and Davos, Switzerland, New York, NY, Denver, Colo, Padua, Italy, and Bethesda, Md*

Changes in the composition, metabolic activity, or both of the gut, lung, and skin microbiomes have been associated with asthma, AD, and food allergy, respectively.



**Probiotici :
quando e a chi ?!**

Semin Immunopathol (2017) 39:669–675
DOI 10.1007/s00281-017-0652-y



REVIEW

The maternal microbiome during pregnancy and allergic disease in the offspring

Peter J Vuillermin^{1,2,3,4} • Laurence Macia⁵ • Ralph Nanan⁵ • Mimi LK Tang^{3,6} •
Fiona Collier^{1,2,3} • Susanne Brix⁷

There has been a vast amount of work done on the infant microbiome, but the **maternal microbiome during pregnancy remains relatively underinvestigated, particularly in humans**, and may be of **fundamental importance to the prevention of allergic disease and asthma in the modern environment.**

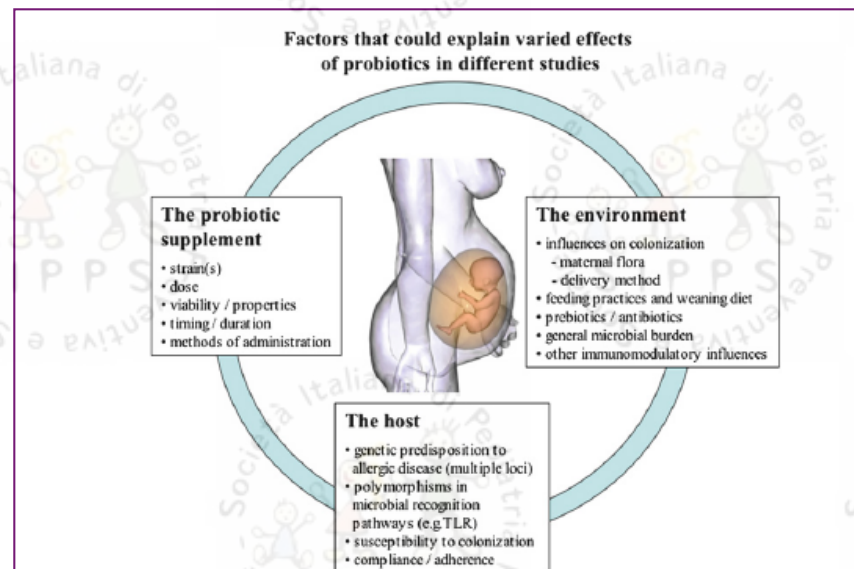


FIG 1. Factors that could explain the varied effects of probiotics.

Prevenzione con probiotici in gravidanza, allattamento e nel neonato

Fiocchi et al. *World Allergy Organization Journal* (2015) 8:4
DOI 10.1186/s40413-015-0055-2



POSITION ARTICLE AND GUIDELINES

Open Access

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics

Alessandro Fiocchi^{1†}, Ruby Pawankar^{2†}, Carlos Cuello-Garcia^{3,4}, Kangmo Ahn⁵, Suleiman Al-Hammadi⁶, Arnav Agarwal^{3,7}, Kirsten Beyer⁸, Wesley Burks⁹, Giorgio W Canonica¹⁰, Motohiro Ebisawa¹¹, Shreyas Gandhi^{3,7}, Rose Kamenwa¹², Bee Wah Lee¹³, Haiqi Li¹⁴, Susan Prescott¹⁵, John J Riva¹⁶, Lanny Rosenwasser¹⁷, Hugh Sampson¹⁸, Michael Spigler¹⁹, Luigi Terracciano²⁰, Andrea Vereda-Ortiz²², Susan Wasserman²¹, Juan José Yepes-Nuñez³, Jan L Brożek^{3,21*} and Holger J Schünemann^{3,21}

Results:the WAO guideline panel determined that there is a likely net benefit from using probiotics resulting primarily from prevention of eczema.

The WAO guideline panel suggests:

- a) using probiotics in **pregnant women** at high risk for having an allergic child;
- b) using probiotics in **women who breastfeed** infants at high risk of developing allergy;
- c) using probiotics in **infants** at high risk of developing allergy.

L'ambiente microbico perinatale modula il sistema immunitario e la comparsa delle allergie

COLONISATION OF THE GUT BY BIFIDOBACTERIA IS MUCH MORE COMMON IN VAGINAL DELIVERIES THAN CAESAREAN SECTIONS.

Musilova S1, Rada V, Vlkova E, Bunesova V, Nevoral J. *Acta Paediatr.* 2015 Jan 20.

I bambini nati attraverso il taglio cesareo hanno un'elevata incidenza di distress respiratorio ed un alto rischio di asma, atopia, obesità e diabete di tipo 1



Effect of formula containing *Lactobacillus reuteri* DSM 17938 on fecal microbiota of infants born by cesarean-section.

Garcia Rodenas J. *Pediatr. Gastroenterol. Nutr.* 63, 681–687. (2016).

Treating babies with ***L. reuteri* DSM 17938** from 2 weeks to 4 months of age modulated the development of gut microbiota toward the community pattern found in vaginally delivered infants

PROBIOTICO : EFFETTI CEPPO SPECIFICI

BREAKING NEWS



ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in
Biotechnology

Identification of probiotic effector molecules: present state and future perspectives

Sarah Lebeer¹, Peter A Bron², Maria L Marco³, Jan-Peter Van Pijkeren⁴, Mary O'Connell Motherway⁵, Colin Hill⁵, Bruno Pot^{6,7}, Stefan Roos⁸ and Todd Klaenhammer⁹



Current Opinion in Biotechnology 2018, 49:217–223

While the major part of the manuscript is focused on probiotic mechanisms of action from a microbiological perspective, possible molecular mechanisms of action of probiotics

Various probiotic effector molecules have been identified that mediate specific aspects of probiotic modes of action.

Complexity of probiotics as live microorganisms with their **hundreds or thousands** of probably bioactive effector molecules should be embraced.

Lactobacillus reuteri may act as a “microbial antihistamine”

Diacylglycerol kinase synthesized by commensal *Lactobacillus reuteri* diminishes protein kinase C phosphorylation and histamine-mediated signaling in the mammalian intestinal epithelium

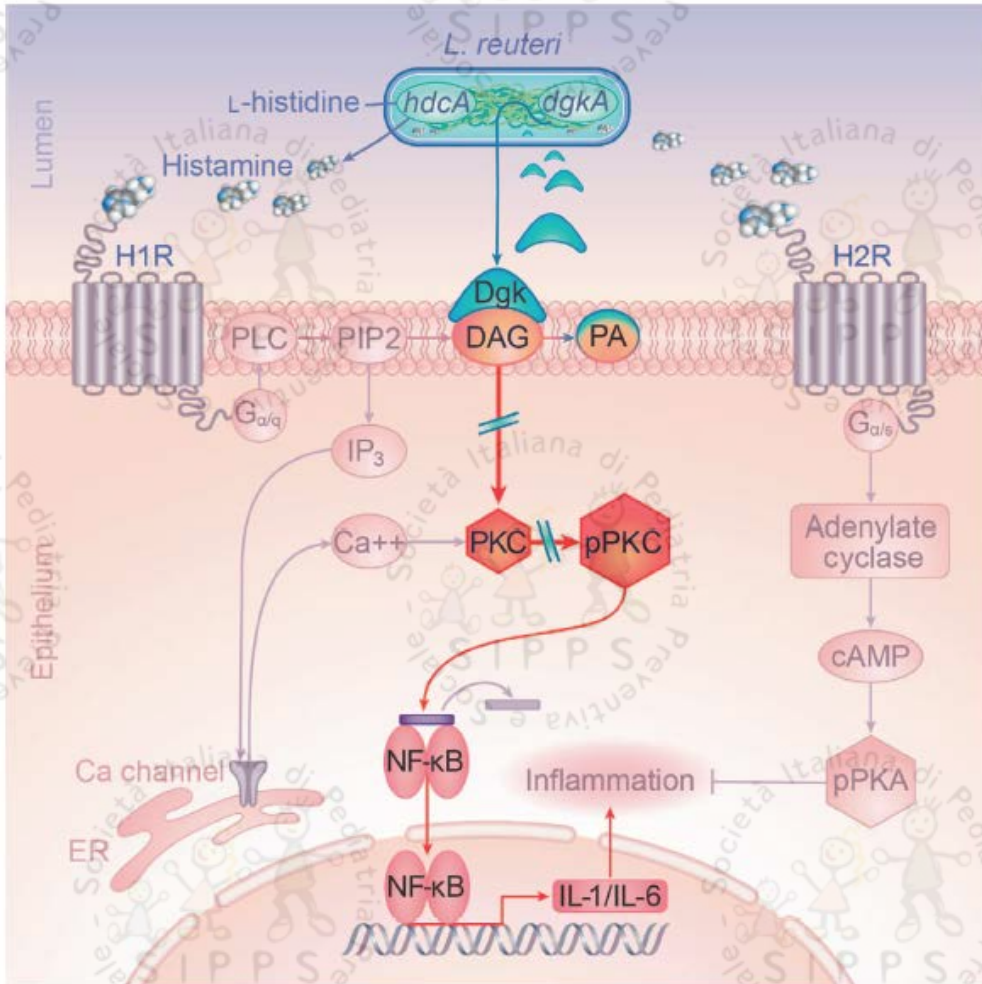
BREAKING NEWS

BP Ganesh^{1,2,3}, A Hall^{1,2}, S Ayyaswamy^{1,2}, JW Nelson⁴, R Fultz^{2,4}, A Major^{1,2}, A Haag², M Esparza^{1,2},²

Mucosal Immunology
OFFICIAL JOURNAL OF THE SOCIETY FOR MUCOSAL IMMUNOLOGY

2017

Induzine di DAG KINASI



Lactobacillus reuteri act generating “microbial antihistamine factors” like DAG kinase may abrogate intestinal inflammation (H1R mediated) and promote the development of new microbiome-harvested treatment strategies.



Human-derived <i>Lactobacillus reuteri</i>		Histamine*	Presence of Histidine Decarboxylase Related Genes [†]			
			<i>hdcP</i>	<i>hdcA</i>	<i>hdcB</i>	<i>hisS2</i>
MLSA Clade II	DSM 20016	0.625	√	√	√	√
	ATCC PTA 4659	0.971	√	√	√	√
	ATCC PTA 5289	0.932	√	√	√	√
	ATCC PTA 6475	1.000	√	√	√	√
	CF15-6	0.469	√	√	√	√
	CF4-6g	0.844	√	√	√	√
	JCM 1112	0.544	√	√	√	√
	LMS11-1	0.612	√	√	√	√
	LMS11-3	0.487	√	√	√	√
	MM3-1a	0.660	√	√	√	√
	SR-11	0.191	√	-	-	√
	SR-14	0.008	√	-	-	√
	MLSA Clade VI	ATCC 55730	0.000	-	-	-
CF48-3A		0.003	-	-	-	-
CF6-2a		0.001	-	-	-	-
DSM 17938		0.000	-	-	-	-
M27U15		0.004	-	-	-	-
M45R2		0.445	√	√	√	√
M81R43		0.000	-	-	-	√
MF14-C		0.000	-	-	-	-
MF2-3		0.192	-	-	-	-
MM34-4a		0.001	-	-	-	-
MM36-1a		0.487	√	√	√	√
MV36-2a		0.000	-	-	-	√
MV4-1a		0.005	-	-	-	-

Fare la scelta corretta tra probiotici composti da uno o più ceppi

Probiotici : quali ?! Singolo ceppo Vs mix di ceppi

...the immunoregulatory actions of certain probiotics can be inhibited in the presence of other strains.

This suggests that the benefits of mixed strain pro-biotic preparations may actually be less than the sum of their parts...

L. B. van der Aa, et al. Clinical & Experimental Allergy, 2010



Fare la scelta corretta tra probiotici composti da uno o più ceppi

Probiotici : quali ?! Singolo ceppo Vs mix di ceppi

PRESENTATION

Effectiveness of Multistrain Versus Single-strain Probiotics *Current Status and Recommendations for the Future*

Arthur C. Ouwehand, PhD, Marcos M. Invernici, PhD,†
Flávia A.C. Furlaneto, PhD,† and Michel R. Messori, PhD†*

(J Clin Gastroenterol 2018;00:000–000)

Some strains of lactic acid bacteria and also probiotics have been documented to produce antimicrobial substances, varying from organic acids to bacteriocins.

.....an antagonistic activity may take place between strains from the same genus, for example, Lactobacillus, in a probiotic formulation



Probiotici ed antibiotico resistenza

Detection of antibiotic resistance in probiotics of dietary supplements

Aloysius Wong¹, Davey Yueh Saint Ngu², Lydia Annabel Dan², Amanda Ooi¹ and Renee Lay Hong Lim^{2*}

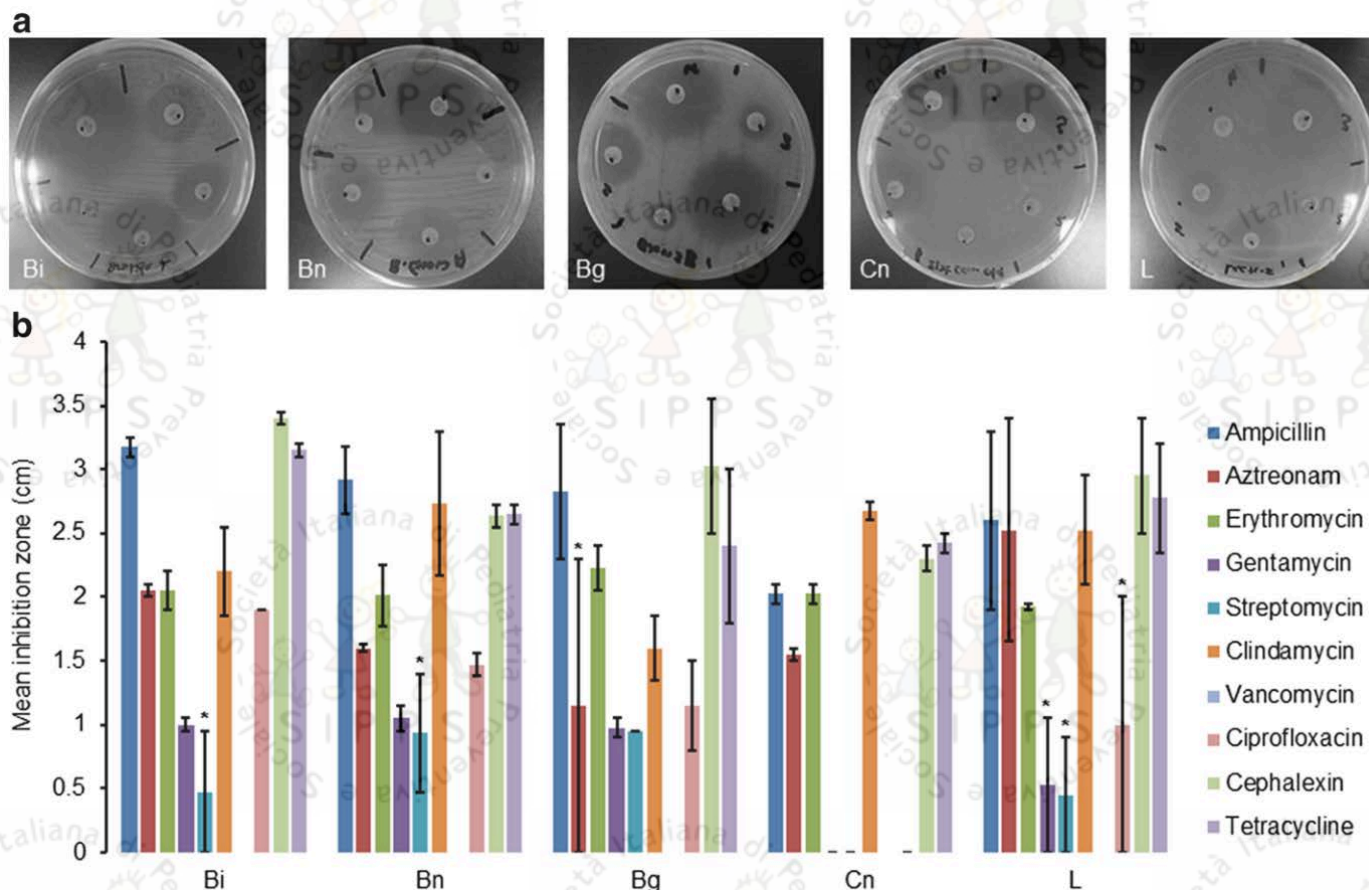


Fig. 2 The antibiotic susceptibility profile of probiotic bacteria in the dietary supplements. **(a)** Representative MRS agar plates of bacteria lawn of Bi, Bn, Bg, Cn and L dietary supplements layered with antibiotic discs showing susceptibility towards multiple antibiotics as characterized by the presence of 'clear' inhibition zones. **(b)** Mean inhibition zones measured from the bacteria lawn of Bi, Bn, Bg, Cn and L dietary supplements layered with the respective antibiotic discs. Error bars represent standard error of the mean ($n \geq 2$) and (*) represents inhibition zone present in only certain batches of bacteria in the respective dietary supplement

Probiotici ed antibiotico resistenza

Removal of antibiotic resistance plasmids from *Lactobacillus reuteri* ATCC 55730 and characterization of the resulting daughter strain *L. reuteri* DSM 17938

Appl. Environ. Microbiol., 2008

Anna Rosander^{1#}, Eamonn Connolly² and Stefan Roos^{1*}

¹Department of Microbiology, Swedish University of Agricultural Sciences, P.O. Box 7025, SE-750 07 Uppsala, Sweden. ²BioGaia AB, P.O. Box 3242, SE - 103 64 Stockholm, Sweden.

- beta-lactam, tetracycline and lincosamide resistance -

A new daughter strain, *L. reuteri* DSM 17938, was derived from **ATCC 55730** by removal of the two plasmids, and it was shown to have lost the resistances associated with them.

NON TUTTI I LACTOBACILLI REUTERI SONO UGUALI

Valutare lo stato di salute dell'individuo prima della prescrizione

Generally, the real risk in using probiotic products is related more to a compromised health status of the patient than to the microbial strain used in the probiotic product.



Summary

As with safety

- Probiotics have been shown to be safe in **immunocompetent** hosts in an outpatient setting.



- Administration of probiotics to **immunocompromised**, chronically ill, hospitalized patients with GI disorders, and indwelling catheters may predispose to **probiotic sepsis**, probiotics may increase translocation of bacteria into the bloodstream.

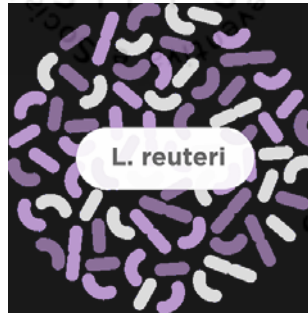
Toscano M, et al. A consumer's guide for probiotics: 10 golden rules for a correct use. *Dig Liver Dis.* 2017

Chernai 2016



- Several studies have assessed the safety of this organism in adults, children, infants, and even in an HIV-infected population
- The results showed that a dose as high as 2.9×10^9 colony-forming units (cfu)/day was still well tolerated, safe, and efficacious in humans. There have also been numerous articles enumerating the benefits of *L. reuteri* as a probiotic. **Front. Microbiol., 19 April 2018**

Lactobacillus Reuteri DSM 17938



Considerazioni conclusive

I probiotici hanno dimostrato un effetto immunoregolatorio (induzione dei Treg) con effetto ceppo specifico

E' possibile ipotizzare un approccio personalizzato con specifici ceppi di probiotici per specifici gruppi di pazienti

Medicina di precisione



Medicina personalizzata

Tailoring probiotic intervention for specific groups