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## MAMP and PRR Interaction at the Centre of Probiotic/Host Interaction

Gwénaél Jan

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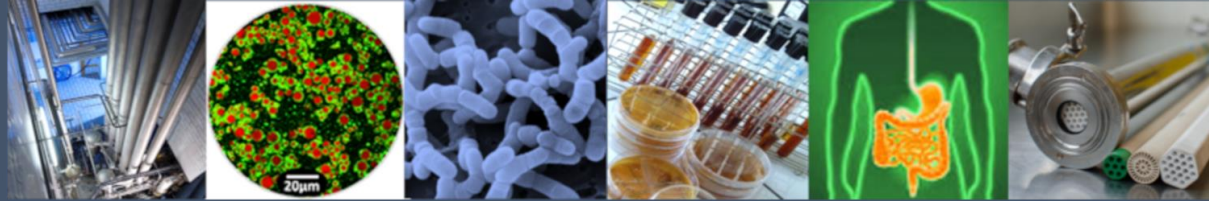
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# MAMPs and PRRs interaction at the center of probiotic/host interaction



**Gwénaél JAN**

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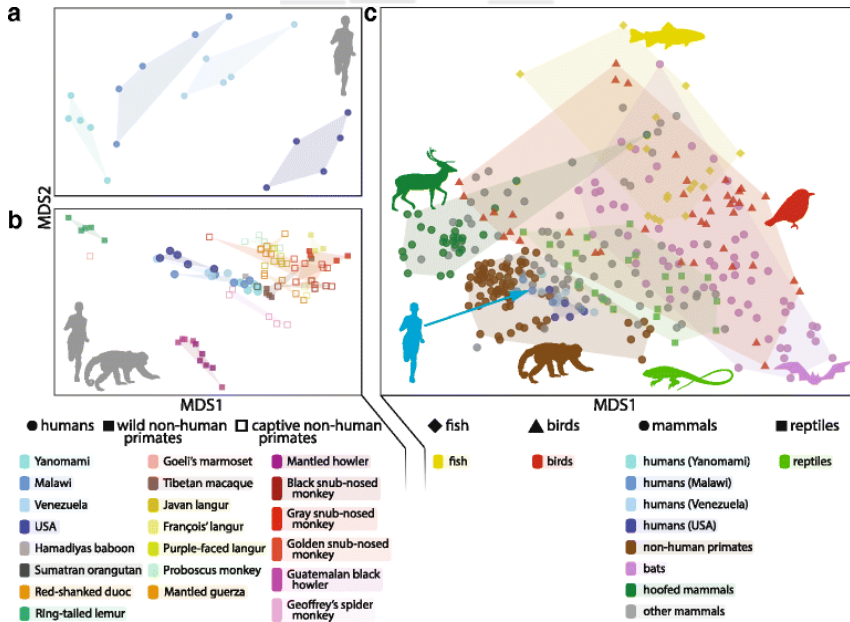




# Microbiota / host interaction, an old story

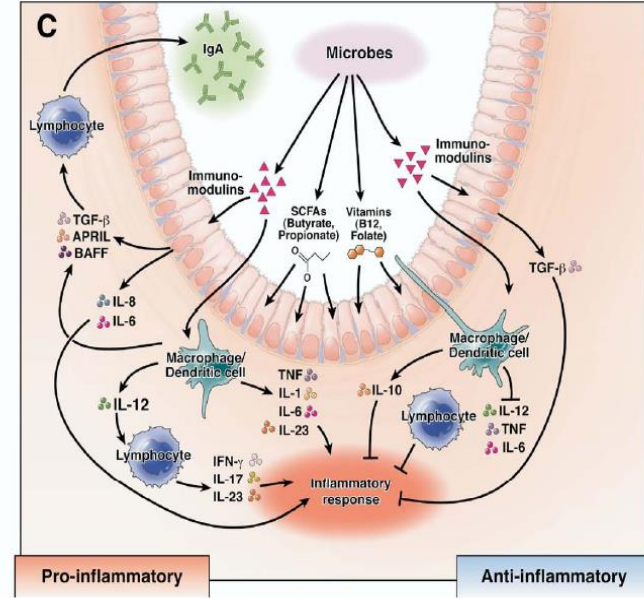


# Coevolution and dependence



Davenport *et al.* BMC Biology (2017)

→ Our microbiota evolved with us

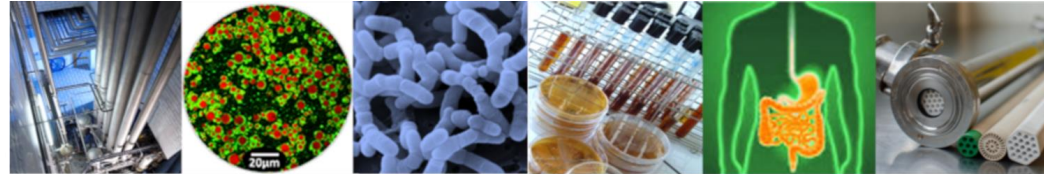


O'Flaherty *et al.* Gut Microbes (2010)

→ And we adapted to its products

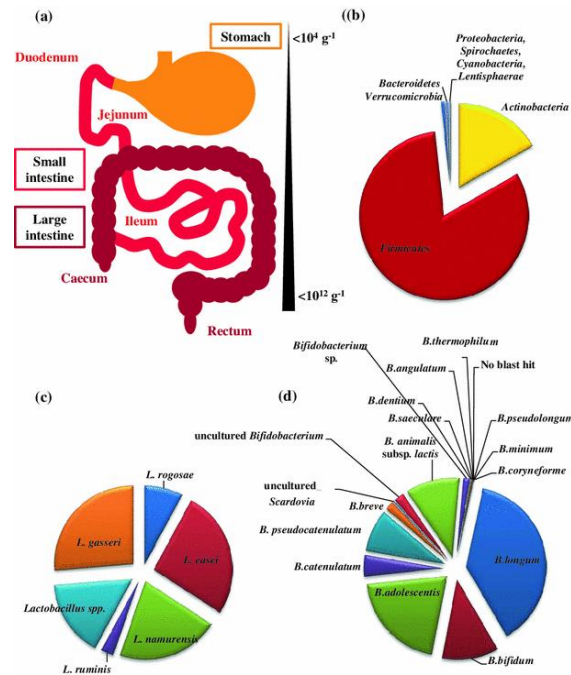
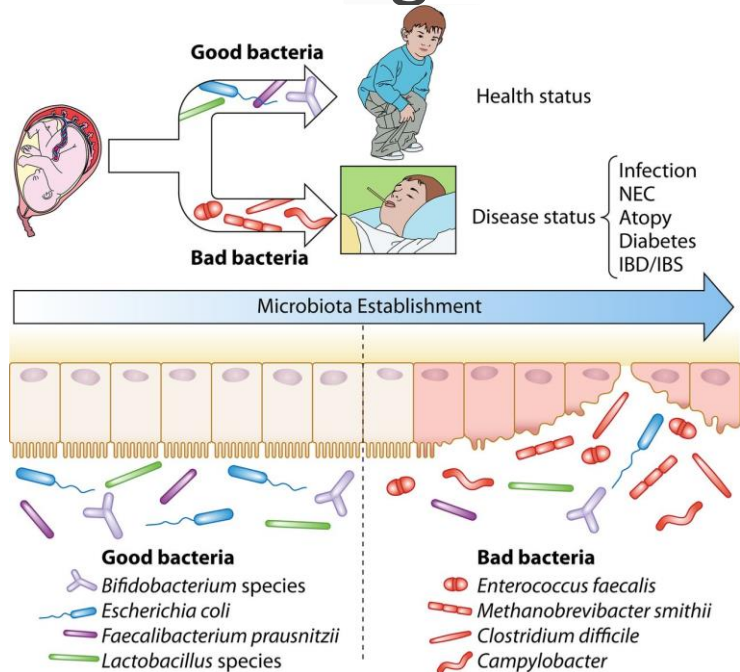


## A key role of the first colonizers



# Main inhabitants and main actors

## Good bugs



Milani *et al.* Microbiol.Mol.Biol.Rev. (2017)

Turroni *et al.* Cell.Mol.Life Sci. (2014)

# Dramatic effects of the absence

## *Bifidobacterium longum* subspecies *infantis*: champion colonizer of the infant gut

Mark A. Underwood<sup>1,2</sup>, J. Bruce German<sup>3,4</sup>, Carlito B. Lebrilla<sup>2,4</sup> and David A. Mills<sup>2,3,5</sup>

Oligosaccharides are abundant in human milk. Production of these highly diverse structures requires significant energy expenditure by the mother and yet these human milk oligosaccharides offer no direct nutritive value to her infant. A primary function of human milk oligosaccharides is to shape the infant's intestinal microbiota with life-long consequences.

***B. infantis* displays anti-inflammatory activity** and result of a large repertoire of bacterial genes encoding an array of glycosidases and oligosaccharide transporters not found in other bacterial species. *In vitro*, *B. infantis* grows better than other bacterial strains in the presence of human milk oligosaccharides, displays anti-inflammatory activity in premature

## *B. infantis* decreases the risk of necrotizing enterocolitis

necrotizing enterocolitis in premature infants. Colonization with *B. infantis* is also associated with increased vaccine responses. Probiotic organisms have historically been selected based on ease of production and stability. The advantages of *B. infantis*, selected through coevolution with human milk glycans, present an opportunity for focused manipulation of the infant intestinal microbiota.

The colonization of the fetal gut begins *in utero* with swallowing of amniotic fluid. At that point, infants begin a life-long relationship with their gut microbiota and its community of milk oligosaccharides (MOS) and gut microbiome) and presumably the health consequences of the phenotype of the gut microbiota occur with rupture of the fetal membranes, birth, initiation of feeding, addition of solid foods, weaning, and interventions such as antibiotics, acid-suppression, and probiotic or probiotic dietary supplements. The predominance of "bifid" microbes in the stools of healthy infants was described more than 100 y ago, prompting the

hypothesis that human milk contained "bifidogenic factors" that stimulated the growth of these bifidobacteria (1).

Probiotics are dietary supplements that promote health benefits by stimulating the growth and/or activity in the gut lumen of commensal microbes (ideally without stimulating potential pathogens). Probiotics include a variety of bacteria and yeasts. A collection of complex prebiotic oligosaccharides found in abundance in human milk and a single bacterial subspecies, *Bifidobacterium longum* subsp. *infantis* (*B. infantis*) unique in its capacity to consume these oligosaccharides. Note that the species *B. longum* has two subspecies: *B. longum* subsp. *infantis*

### INTESTINAL MICROBIOTA

Humans stand at the end of the long evolution of mammals, with differences in milk conspicuous for the volume, number of structures, and complexity of milk oligosaccharides (Figure 1) (2–4). Human milk oligosaccharides (HMOs) are the third largest solid component of human milk (after lactose and fat) even in times of famine (5), and yet these free glycans are not digestible by the infant as the human gut does not produce the glycosidases necessary to cleave the HMO linkages. The obvious evolutionary question is: What benefit is provided to the infant that justifies the mother's tremendous expenditure of energy to produce this complex molecule? The capacity of *B. infantis* to selectively ingest and consume HMOs (6,7). Among multiple microbial species studied, only two genera, *Bifidobacterium* and *Bacteroides*, are able to comprehensively utilize HMOs as a primary food source (Table 1) (8,9). This relative resistance to microbial consumption allows the HMOs to arrive intact in the distal small bowel and the colon where the largest numbers of commensal bacteria thrive.



### RESEARCH ARTICLE

The Journal of Clinical Investigation

## Commensal *Propionibacterium* strain UF1 mitigates intestinal inflammation via Th17 cell regulation

Natalia Williall<sup>1</sup>, ***Propionibacteria* are enriched in breast-fed infants**, David R. Owen,<sup>3</sup> Josef Neu,<sup>4</sup> and Amir Pour Mohamadzadeh<sup>1,2</sup>

<sup>1</sup>Department of Infectious Diseases and Immunology, <sup>2</sup>Division of Gastroenterology, Hepatology & Nutrition, Department of Medicine, <sup>3</sup>Department of Physiological Sciences, <sup>4</sup>Division of Neonatology, Department of Pediatrics, Loyola University Chicago, Maywood, Illinois, USA; <sup>5</sup>Department of Immunology, Loyola University Chicago, Chicago, IL, USA.

### *Propionibacteria* mitigate induced necrotizing enterocolitis

Consumption of ***Propionibacteria* regulate Th17 cells** leading to necrotizing enterocolitis (NEC), which remains a leading cause of morbidity and mortality in preterm infants that this diminution correlates with alterations in the gut microbiota, particularly enrichment of *Propionibacterium* species. Transfaunation of microbiota from HBM-fed preterm infants or a newly identified and cultured *Propionibacterium* strain, P. UF1, to germfree mice conferred protection against pathogen infection and correlated with profound increases in intestinal Th17 cells. The induction of Th17 cells was dependent on bacterial dihydropyrimidinase acetyltransferase (DlaT), a major protein expressed on the P. UF1 surface layer (S-layer). Binding of P. UF1 to its cognate receptor, SIGNR1, on dendritic cells resulted in the regulation of intestinal phagocytes. Importantly, transfer of P. UF1 profoundly mitigated induced NEC-like injury in neonatal mice. Together, these results mechanistically elucidate the protective effects of HBM and P. UF1-induced immunoregulation, which safeguard against proinflammatory diseases, including NEC.

<sup>1</sup>Department of Pediatrics, University of California, Davis, Sacramento, California; <sup>2</sup>Foods for Health Institute, University of California, Davis, California; <sup>3</sup>Department of Food Science and Technology, University of California, Davis, California; <sup>4</sup>Department of Chemistry, University of California, Davis, California; <sup>5</sup>Department of Microbiology and Immunology, University of California, Davis, California. Correspondence: Mark A. Underwood (mark.underwood@ucdavis.edu)

Received 14 April 2014; accepted 4 August 2014; advance online publication 5 November 2014; doi:10.1038/nri.2014.156



# Healing effect of probiotics



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Clinical Investigation

Article



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## Probiotics (*Lactobacillus acidophilus* and *Bifidobacterium bifidum*) prevent NEC in VLBW infants fed breast milk but not formula

Andreas Repa<sup>1</sup>, Margarita Thanhaeuser<sup>1</sup>, David Endress<sup>2</sup>, Michael Weber<sup>3</sup>, Alexandra Kreissl<sup>1</sup>, Christoph Binder<sup>1</sup>, Angelika Berger<sup>1</sup> and Nadja Haiden<sup>1</sup>

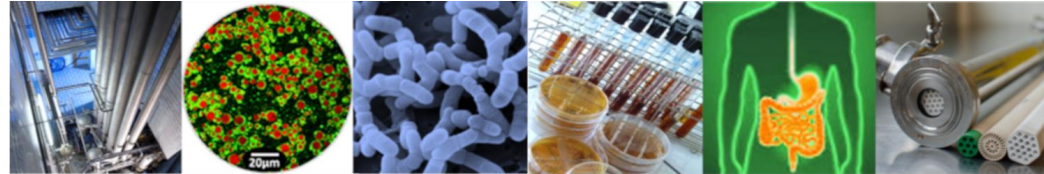
## The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota

Christian Milani,<sup>a</sup> Sabrina Duranti,<sup>a</sup> Francesca Bottacini,<sup>b</sup> Eoghan Casey,<sup>b</sup> Francesca Turroni,<sup>a,c</sup> Jennifer Mahony,<sup>b</sup> Clara Belzer,<sup>d</sup> Susana Delgado Palacio,<sup>e</sup> Silvia Arboleya Montes,<sup>e</sup> Leonardo Mancabelli,<sup>a</sup> Gabriele Andrea Lugli,<sup>a</sup> Juan Miguel Rodriguez,<sup>f</sup> Lars Bode,<sup>g</sup> Willem de Vos,<sup>d,h</sup> Miguel Gueimonde,<sup>e</sup> Abelardo Margolles,<sup>e</sup> Douwe van Sinderen,<sup>b</sup> Marco Ventura<sup>a,c</sup>

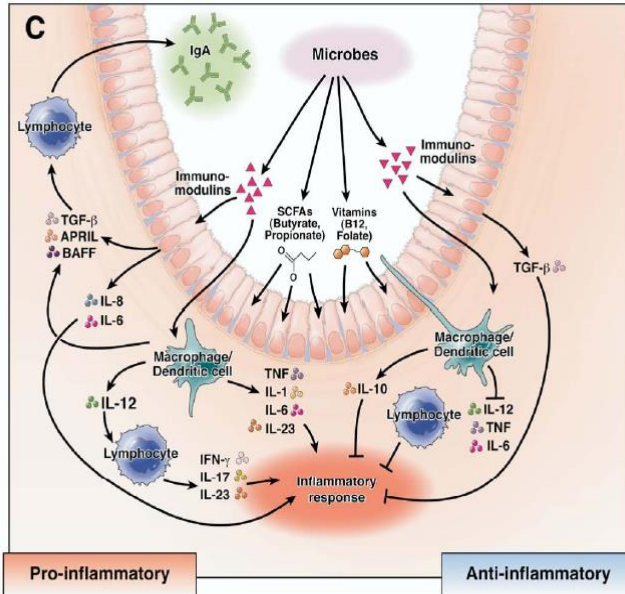




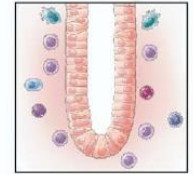
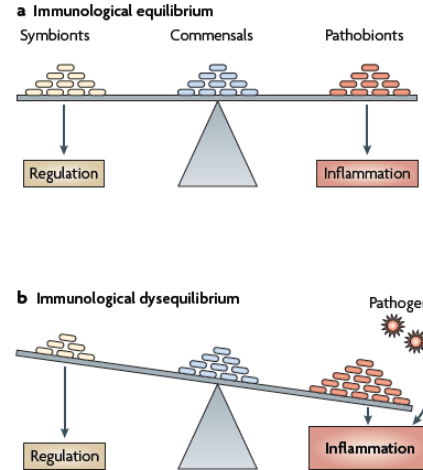
# The gut microbiota and inflammation



# Pro- and anti-inflammatory bugs



O'Flaherty *et al.* Gut Microbes (2010)



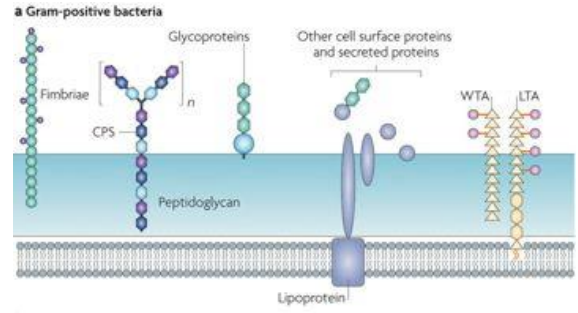
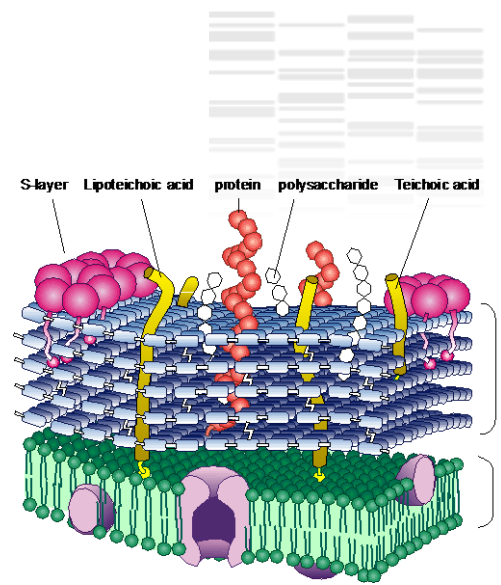
“Physiological” or “controlled” inflammation



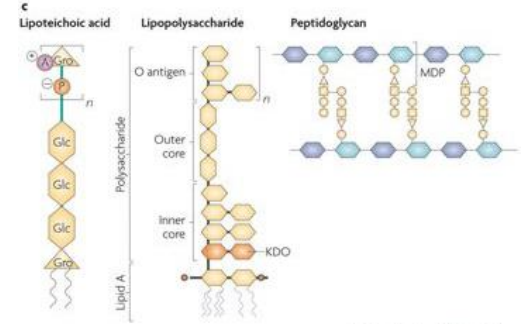
# Microbial Associated Molecular Patterns / Pattern Recognition Receptors



# MAMPs : Gram-positive surface



Lebeer *et al.* Nature Reviews (2010)



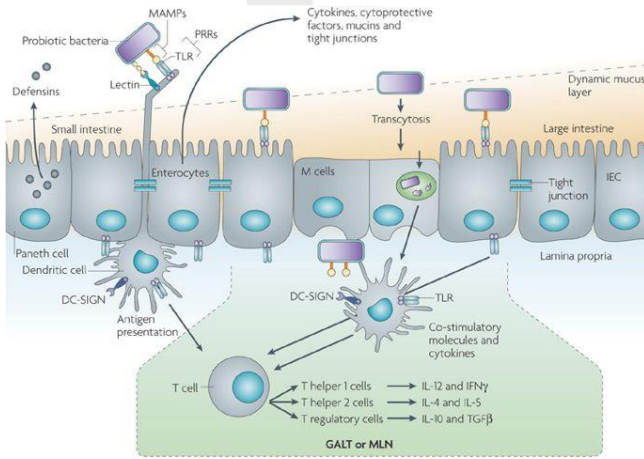
Nature Reviews | Microbiology

Lebeer *et al.* Nature Reviews (2010)

→ Macromolecules and glycobiome

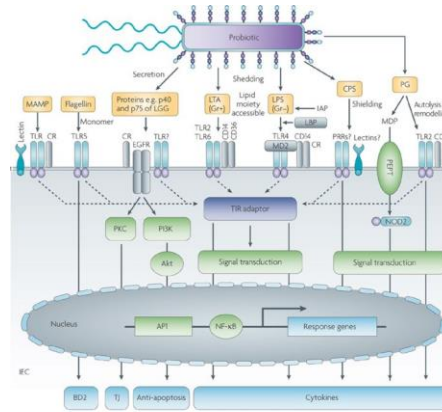
→ Decorated with many motives

# PRRs: host receptors



Lebeer *et al.* Nature Reviews (2010)

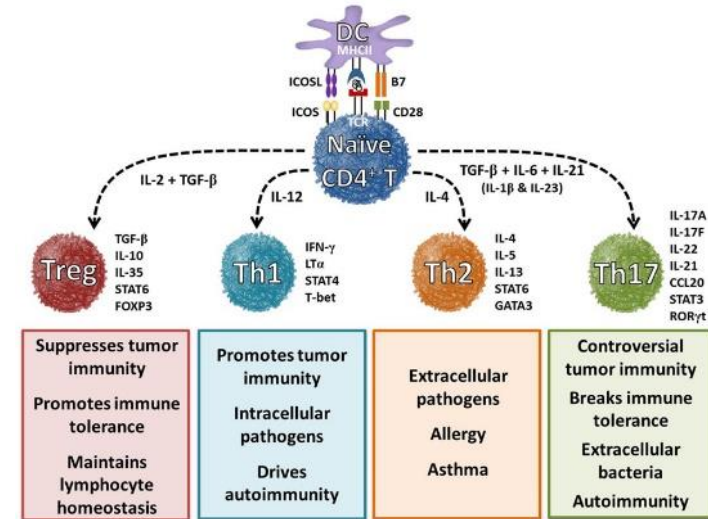
→ Immune or epithelial cells



Nature Reviews | Microbiology

Lebeer *et al.* Nature Reviews (2010)

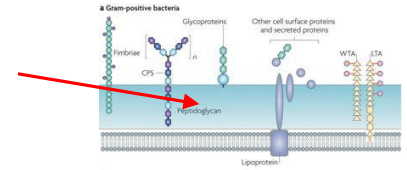
→ Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs)



Bailey *et al.* Front. Immunol. (2014)

→ Different immunomodulatory effects

# Example of *Lactobacillus salivarius* PG

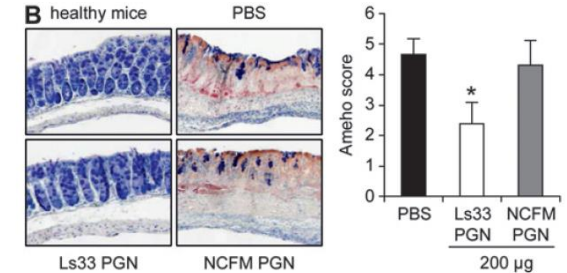


## Inflammatory bowel disease

### Anti-inflammatory capacity of selected lactobacilli in experimental colitis is driven by NOD2-mediated recognition of a specific peptidoglycan-derived muropeptide

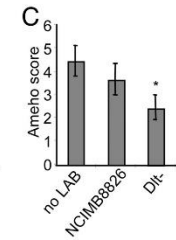
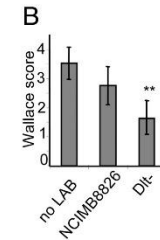
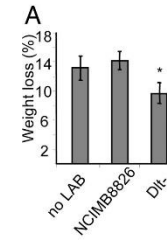
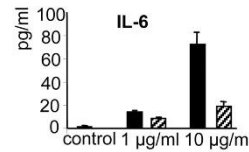
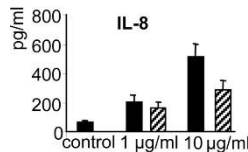
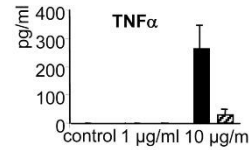
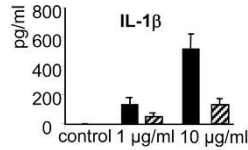
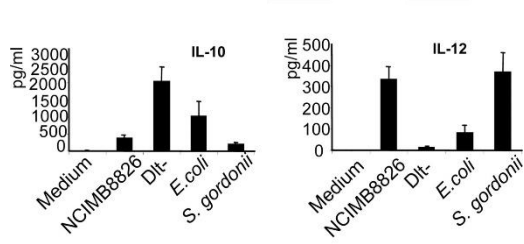
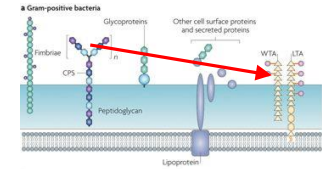
Elise Macho Fernandez,<sup>1</sup> Véronique Valenti,<sup>1</sup> Christoph Rockel,<sup>2</sup> Corinna Hermann,<sup>2</sup> Bruno Pot,<sup>1</sup> Ivo Gomperts Boneca,<sup>3,4</sup> Corinne Grangette<sup>1</sup>

**Results** The protective capacity of strain *Lactobacillus salivarius* Ls33 was correlated with a local IL-10 production and was abolished in *Nod2*-deficient mice. PGN purified from Ls33 rescued mice from colitis in an IL-10-dependent manner and favoured the development of CD103<sup>+</sup> DCs and CD4<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells. In



**Figure 4** Peptidoglycan (PGN) from selected strains rescues mice from trinitrobenzene sulfonic acid (TNBS)-induced colitis. BALB/c mice were injected intraperitoneally with phosphate-buffered saline (PBS; n=10), 50 µg (n=5) or 200 µg (n=10) of PGN from Ls33 (Ls33 PGN) or NCFM (NCFM PGN) before induction of colitis. (A) Wallace score evaluated 2 days after induction of colitis. (B) Ameho scores illustrated with representative sections of the distal colon of healthy mice or mice with TNBS-induced colitis, injected intraperitoneally with PBS or 200 µg of PGNs (original magnification, ×20). Data represent mean values with the SEM (\*p<0.05; \*\*p<0.01; \*\*\*p<0.001 vs PBS-treated mice).

# Example of *Lactobacillus plantarum* LTA



Mutation of Dlt reduces D-Ala in TA and makes *L. plantarum* induce IL-10 in PBMCs

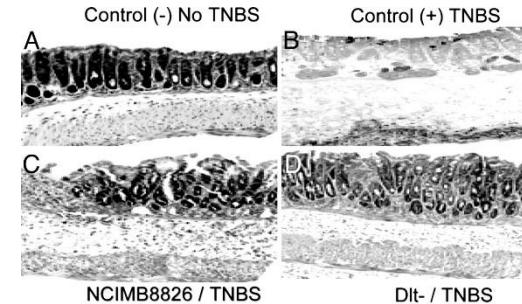
TA from WT induce pro-inflammatory cytokines, while TA from Dlt mutant does not

## Enhanced antiinflammatory capacity of a *Lactobacillus plantarum* mutant synthesizing modified teichoic acids

Corinne Grangette<sup>\*†</sup>, Sophie Nutten<sup>\*‡</sup>, Emmanuelle Palumbo<sup>§</sup>, Siegfried Morath<sup>¶</sup>, Corinna Hermann<sup>¶</sup>, Joelle Dewulf<sup>\*</sup>, Bruno Pot<sup>\*</sup>, Thomas Hartung<sup>¶</sup>, Pascal Hols<sup>§</sup>, and Annick Mercenier<sup>\*‡</sup>

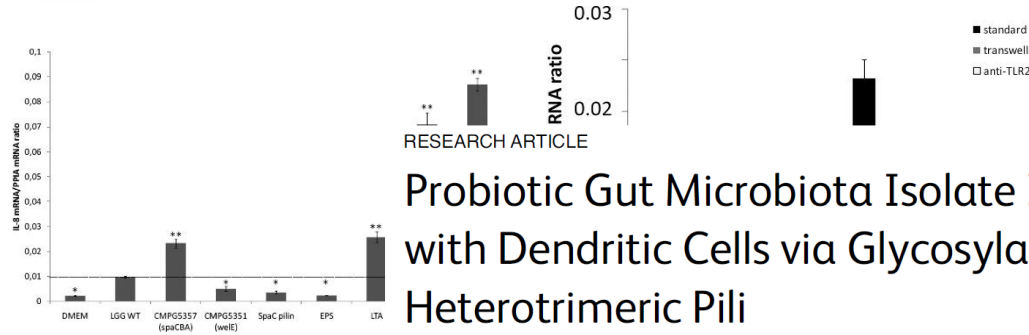
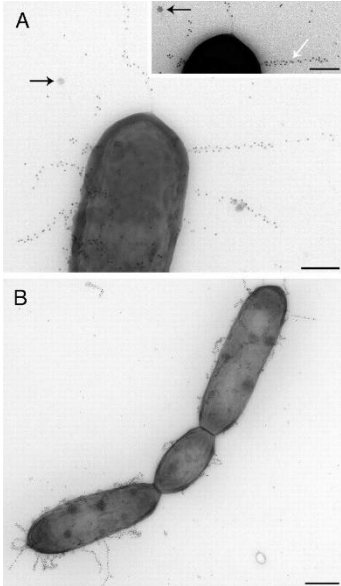
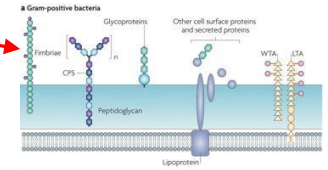
<sup>\*</sup>Laboratoire de Bactériologie des Ecosystèmes, Institut Pasteur de Lille-Institut de Biologie de Lille, 59019 Lille Cedex, France; <sup>†</sup>Unité de Génétique, Institut des Sciences de la Vie, Université Catholique de Louvain, B-1348 Louvain-la-Neuve, Belgium; and <sup>‡</sup>Department of Biochemical Pharmacology, Konstanz University, 78457 Konstanz, Germany

Communicated by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, May 18, 2005 (received for review November 19, 2004)



Mutation of Dlt mutant protects more than WT *plantarum* against colitis

# Example of *Lactobacillus rhamnosus* pili



The pili- mutant induces more inflammatory IL-8



Functional Analysis of *Lactobacillus rhamnosus* GG Pili in Relation to Adhesion and Immunomodulatory Interactions with Intestinal Epithelial Cells

Sarah Lebeer,<sup>a,b</sup> Ingmar Claes,<sup>a</sup> Hanne L. P. Tytgat,<sup>a</sup> Tine L. A. Verhoeven,<sup>a</sup> Eyra Marien,<sup>a</sup> Ingemar von Ossowski,<sup>c</sup> Justus Reunanen,<sup>c</sup> Alri Palva,<sup>c</sup> Willem M. de Vos,<sup>c,d</sup> Sigrid C. J. De Keersmaecker,<sup>a</sup> and Jos Vanderleyden<sup>a</sup>

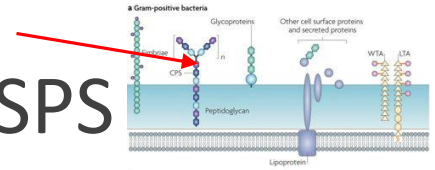
Centre of Microbial and Plant Genetics, K.U. Leuven, Leuven, Belgium<sup>a</sup>; Department of Bioscience Engineering, University of Antwerp, Antwerp, Belgium<sup>b</sup>; Department of Veterinary Biosciences, University of Helsinki, Helsinki, Finland<sup>c</sup>; and Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands<sup>d</sup>

## Probiotic Gut Microbiota Isolate Interacts with Dendritic Cells via Glycosylated Heterotrimeric Pili

Hanne L. P. Tytgat<sup>1,2,3</sup>, Nienke H. van Teijlingen<sup>4</sup>, Ruby May A. Sullan<sup>5\*</sup>, François P. Douillard<sup>6</sup>, Pia Rasinkangas<sup>6</sup>, Marcel Messing<sup>7</sup>, Justus Reunanen<sup>6</sup>, Reetta Satokari<sup>6</sup>, Jos Vanderleyden<sup>1</sup>, Yves F. Dufrêne<sup>3</sup>, Teunis B. H. Geijtenbeek<sup>4</sup>, Willem M. de Vos<sup>3,6,7</sup>, Sarah Lebeer<sup>1,2\*</sup>



# Example of *Bifidobacterium bifidum* CSPS

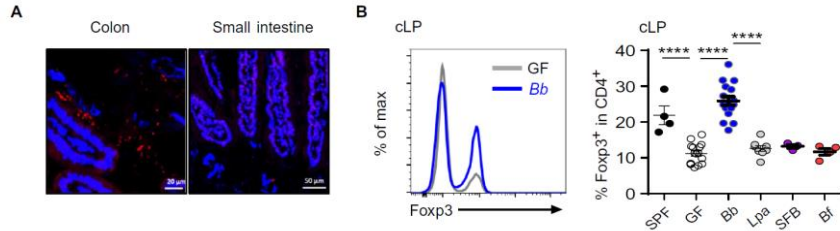


SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

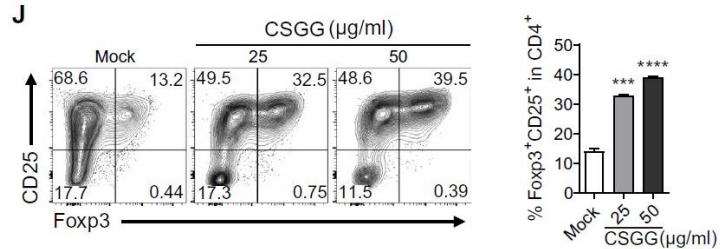
## MICROBIOME

### Cell surface polysaccharides of *Bifidobacterium bifidum* induce the generation of Foxp3<sup>+</sup> regulatory T cells

Ravi Verma<sup>1</sup>, Changhon Lee<sup>2</sup>, Eun-Ji Jeun<sup>2</sup>, Jaew Yi<sup>2</sup>, Kwang Soon Kim<sup>1</sup>, Ambarnil Ghosh<sup>1</sup>, Seohyun Byun<sup>2</sup>, Choong-Gu Lee<sup>1</sup>, Hye-Ji Kang<sup>1</sup>, Gi-Cheon Kim<sup>1</sup>, Chang-Duk Jun<sup>3</sup>, Gwenaël Jan<sup>4</sup>, Chang-Hee Suh<sup>5</sup>, Ju-Yang Jung<sup>5</sup>, Jonathan Sprent<sup>2,6</sup>, Dipayan Rudra<sup>1,2</sup>, Cristina De Castro<sup>7,8</sup>, Antonio Molinaro<sup>8,9</sup>, Charles D. Surh<sup>1,2</sup>, Sin-Hyeog Im<sup>1,2,\*</sup>

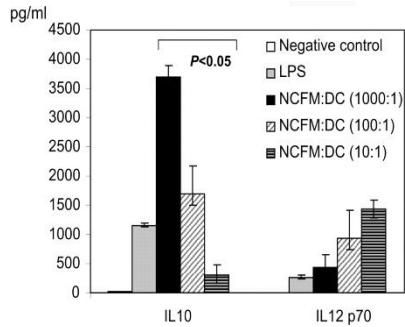
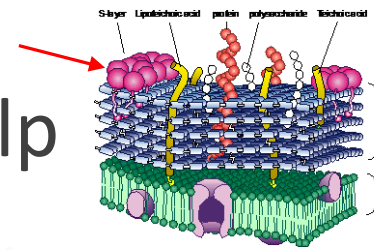


*B. bifidum* monocolonization enhances Treg population in the colon Lamina Propria

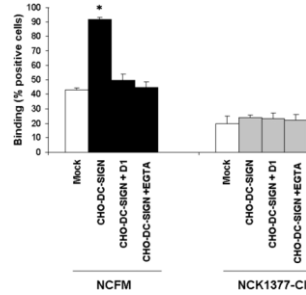


*B. bifidum* surface PS mediates T cell induction

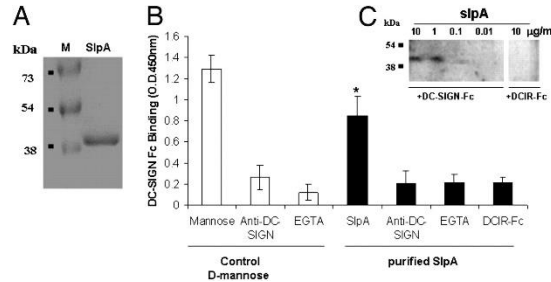
# Example of *Lactobacillus acidophilus* Slp



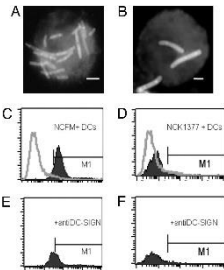
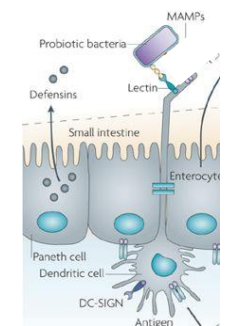
*L. acidophilus* induces IL-10 in immature dendritic cells



*L. acidophilus* binds to DC-SIGN receptors, not the slpA- mutant.



Purified SlpA binds to DC-SIGN receptors



SlpA mediates *L. acidophilus* binding to DC-SIGN receptors

IPNAS

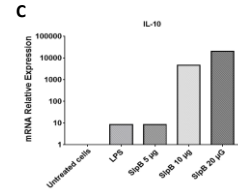
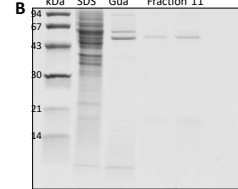
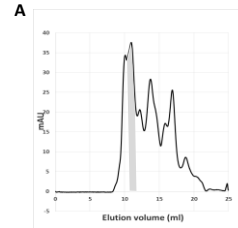
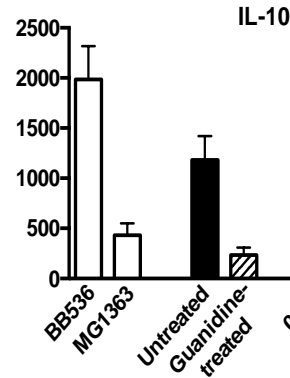
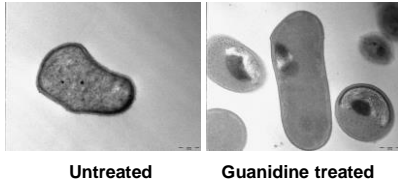
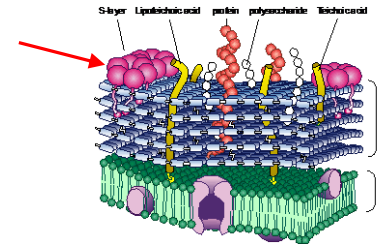
## S layer protein A of *Lactobacillus acidophilus* NCFM regulates immature dendritic cell and T cell functions

Sergey R. Konstantinov<sup>a,b,1</sup>, Hauke Smidt<sup>a</sup>, Willem M. de Vos<sup>a,c</sup>, Sven C. M. Bruijns<sup>b</sup>, Satwinder Kaur Singh<sup>b</sup>, Florence Valence<sup>d</sup>, Daniel Molle<sup>d</sup>, Sylvie Lortal<sup>d</sup>, Eric Altermann<sup>e</sup>, Todd R. Klaenhammer<sup>e,f,2</sup>, and Yvette van Kooyk<sup>b,2</sup>

<sup>a</sup>Laboratory of Microbiology, Wageningen University, Dreijenplein 10, 6703 HB, Wageningen, The Netherlands; <sup>b</sup>VU University Medical Center Amsterdam, v.d. Boelehorststraat 7, 1081 BT Amsterdam, The Netherlands; <sup>c</sup>Department of Basic Veterinary Sciences, Helsinki University, FIN-00014, Helsinki, Finland; <sup>d</sup>Institut National de la Recherche Agronomique, 65 rue de Saint Brieuc, 35000 Rennes, France; and <sup>e</sup>Department of Microbiology and <sup>f</sup>Southeast Dairy Foods Research Center, North Carolina State University, Raleigh, NC 27695

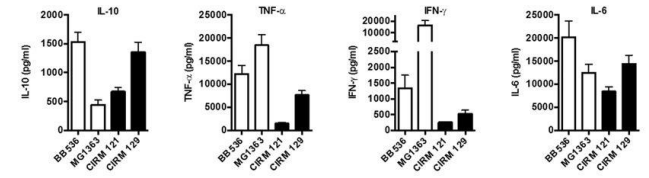
Contributed by Todd R. Klaenhammer. October 15, 2008 (sent for review July 21, 2008)

# *Propionibacterium freudenreichii* SlpB

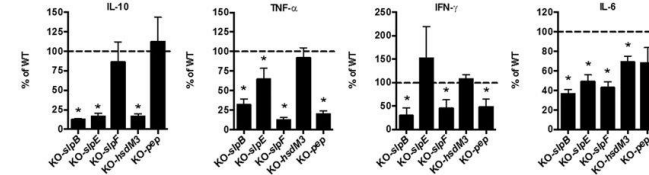


Surface protein SlpB induces production of IL-10 in PBMC cells.

A

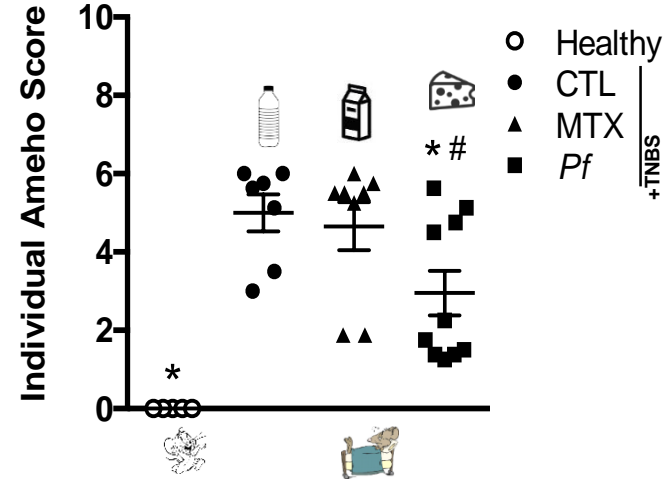
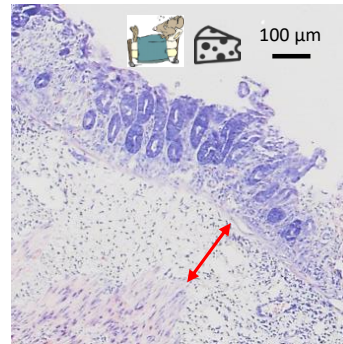
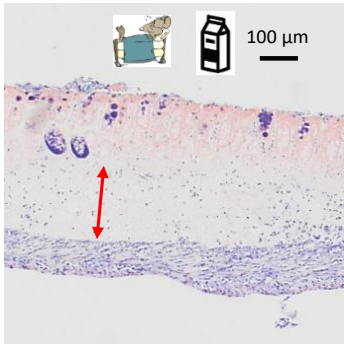
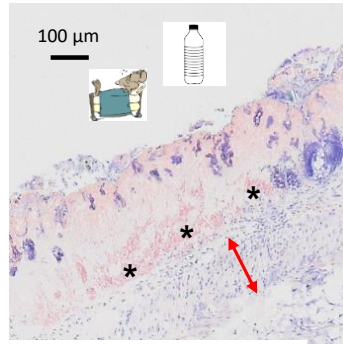
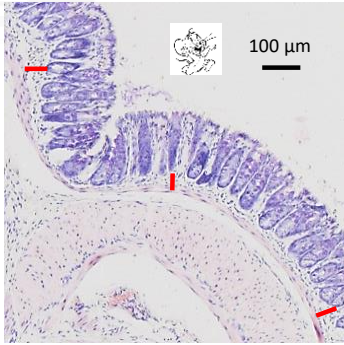


B



Inactivation of SlpB suppresses IL-10 induction

# *P. freudenreichii* cheese in a murine model of colitis





AGRO  
CAMPUS  
OUEST



Food/commensal/probiotic bacteria have various MAMPs

Various immune responses, may be strain-dependent

We can make fermented foods with these strains



Thank  
you for  
your  
attention

Don't ask  
tough  
questions

Houem Rabah

Fillipe Luis Rosa do  
Carmo

Song Huang

Floriane Gaucher  
20<sup>th</sup> June, 11H55,  
Probiotics for health

