Terrassa, 19 de Octubre de 2018

CRITERIOS DE EFICACIA Y SEGURIDAD DE LOS PROBIÓTICOS

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Microbiome and Probotics in 1885

» Souvent, dans nos causeries du laboratoire, depuis bien des années, j'ai parlé, aux jeunes savants qui m'entouraient, de l'intérêt qu'il y aurait à nourrir un jeune animal (lapin, cobaye, chien, poulet), dès sa naissance, avec des matières nutritives *pures*. Par cette dernière expression, j'entends désigner des produits alimentaires qu'on priverait artificiellement et complètement des microbes communs.

» Sans vouloir rien affirmer, je ne cache pas que j'entreprendrais cette étude, si j'en avais le temps, avec la pensée préconçue que la vie, dans ces conditions, deviendrait impossible.

» Si ces genres de travaux se simplifiaient par leur développement même, on pourrait peut-être tenter l'étude de la digestion par l'addition systématique, aux matières nutritives *pures* dont je parle, de tel ou tel microbe simple ou de microbes divers associés bien déterminés.

Louis Pasteur. Comptes Rendus de l'Académie des Sciences, Paris 1885; 100:68

Gut Microbiota and Bowel Motor Function

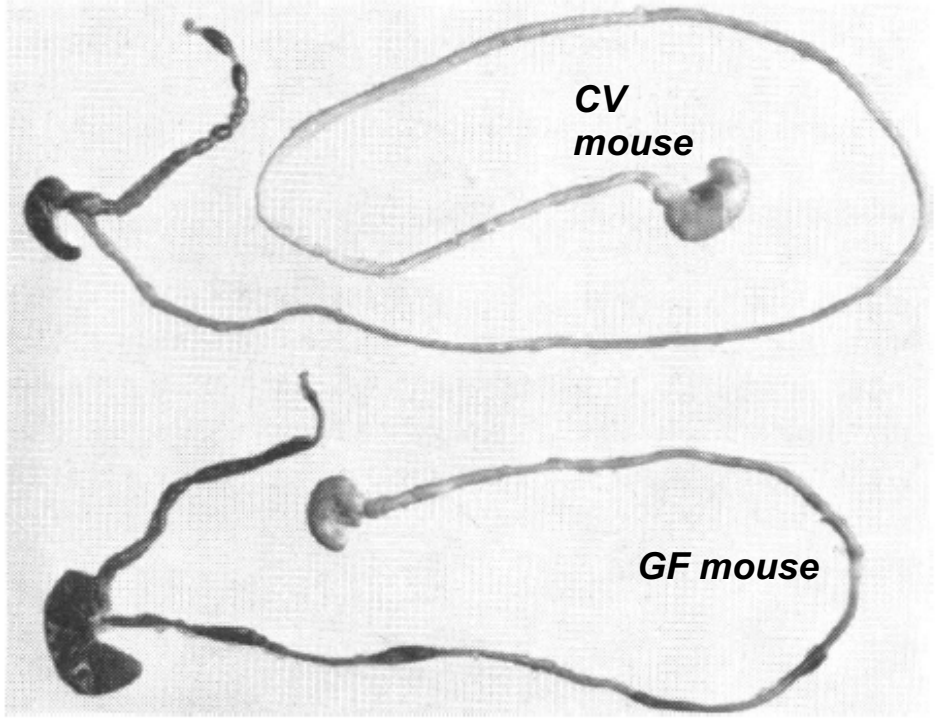
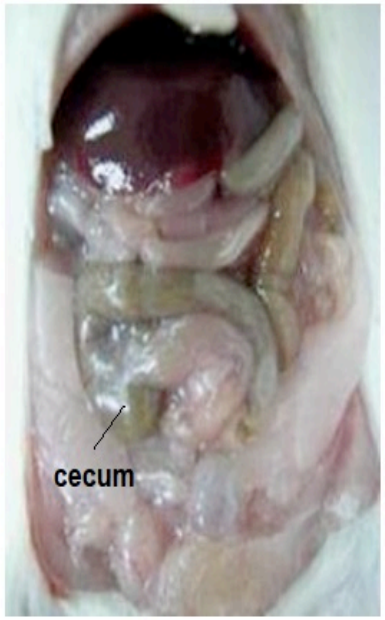
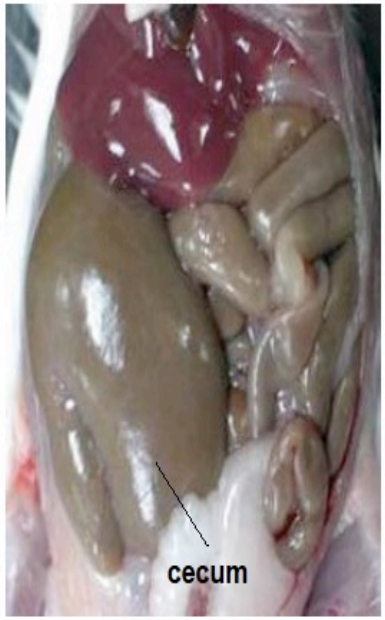


FIG. 1. *Gastrointestinal tract of conventional (above) and germ-free mice fed an aqueous carmine suspension via intragastric tube 6 hr prior to sacrifice. The small intestine of the germ-free animal contains a greater residual amount of dye than does its conventional counterpart. The distended cecum, characteristic of the germ-free mouse, is evident at the left.*



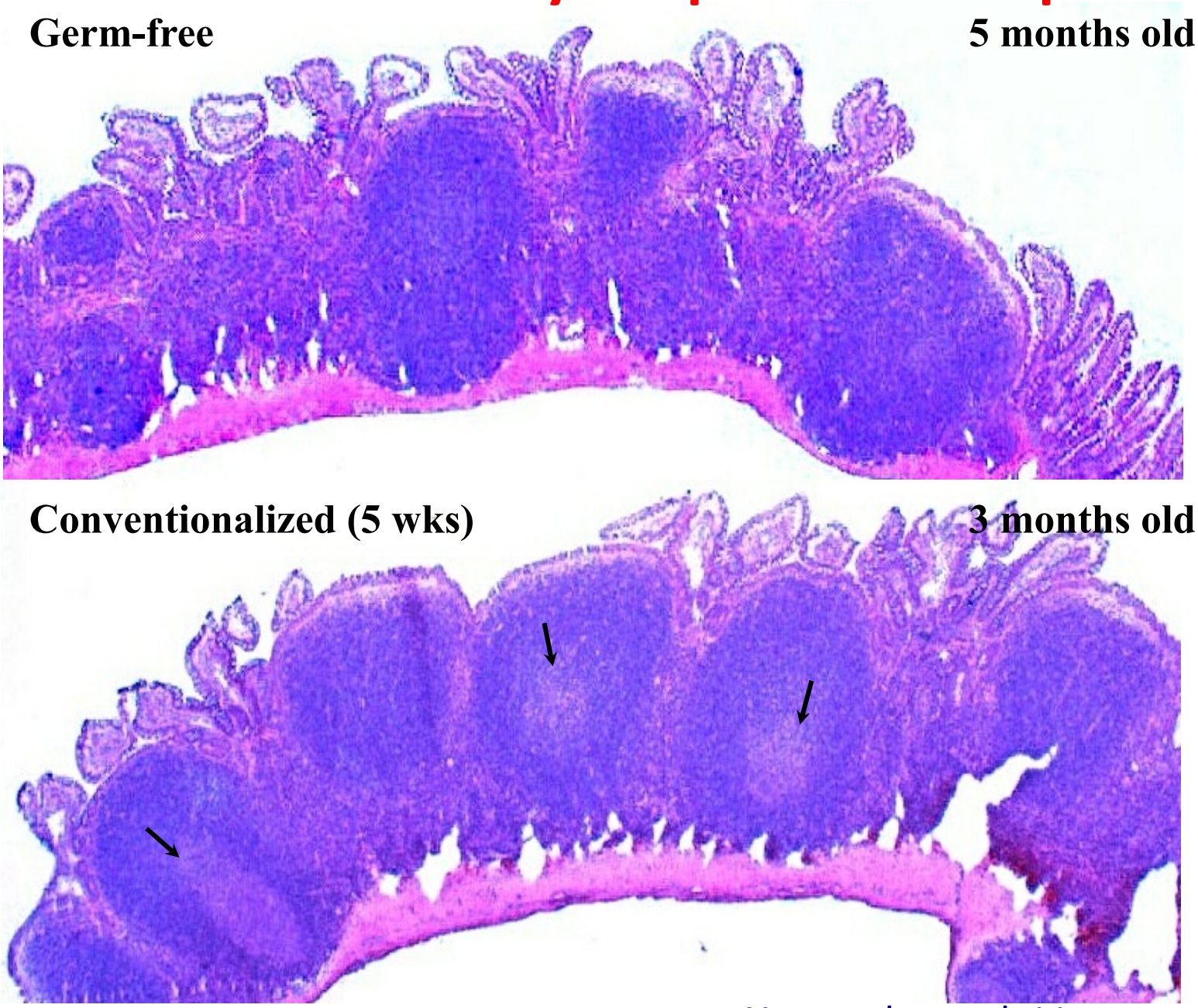
CV mouse



GF mouse

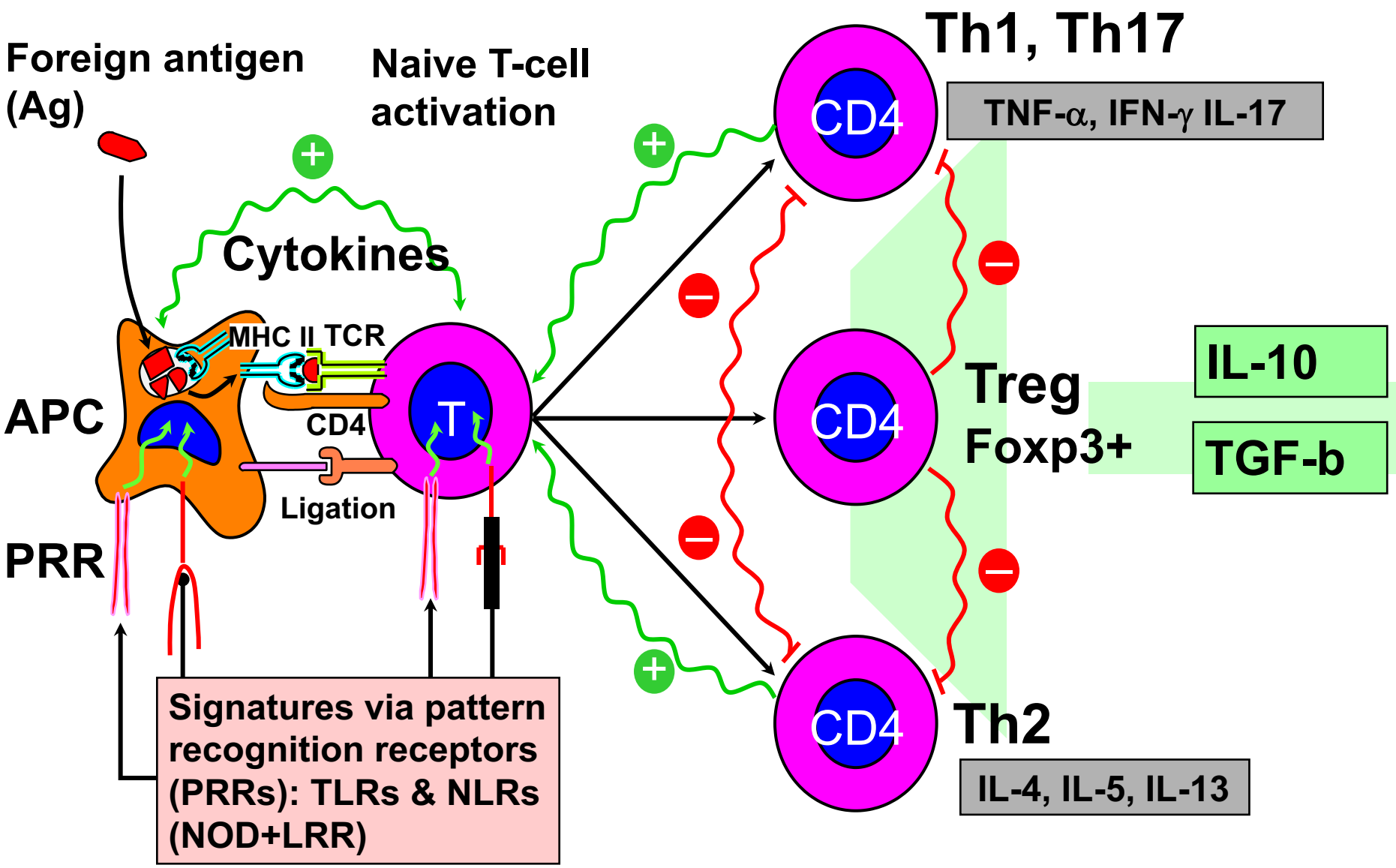
Abrams and Bishop, *J Bacteriol* 1966

Gut bacteria drive Peyer's patch development



Yamanaka et al. J Immunol. 2003

Decision making in the adaptive (acquired) immune system is instructed by the microbial impact on APCs and T cells



By Per Brandtzaeg in Guarner et al, Nature Clin Practice 2006

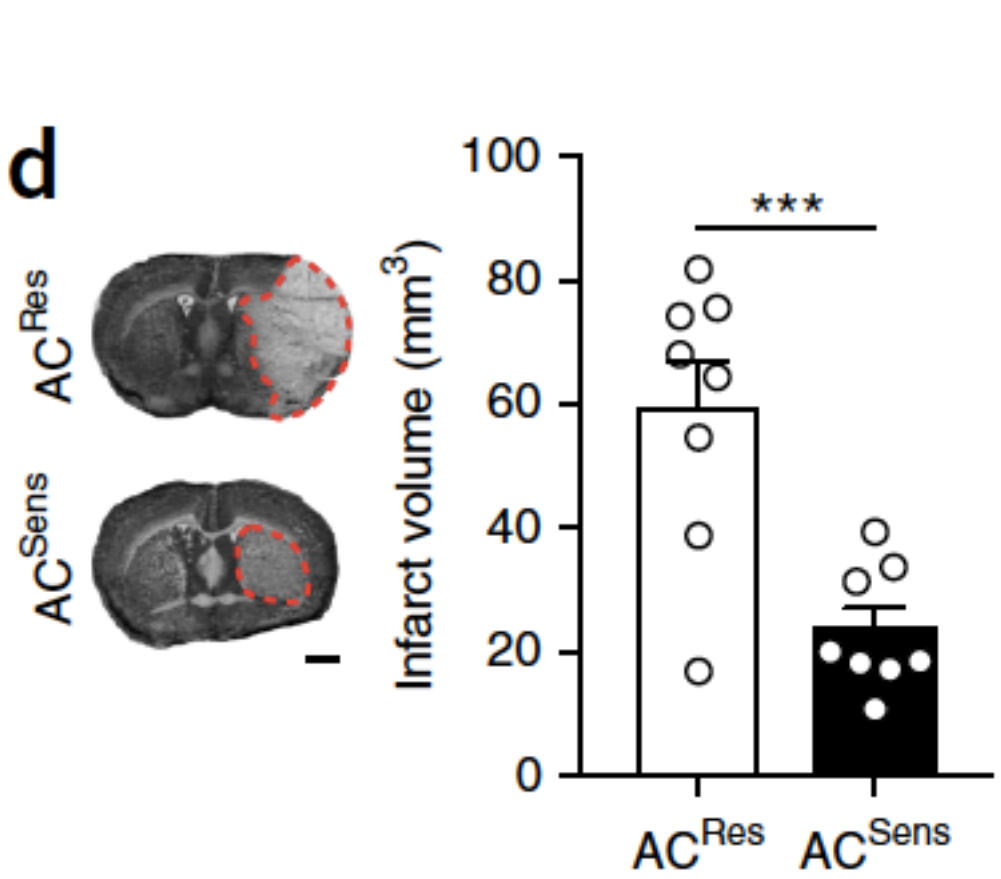
nature medicine

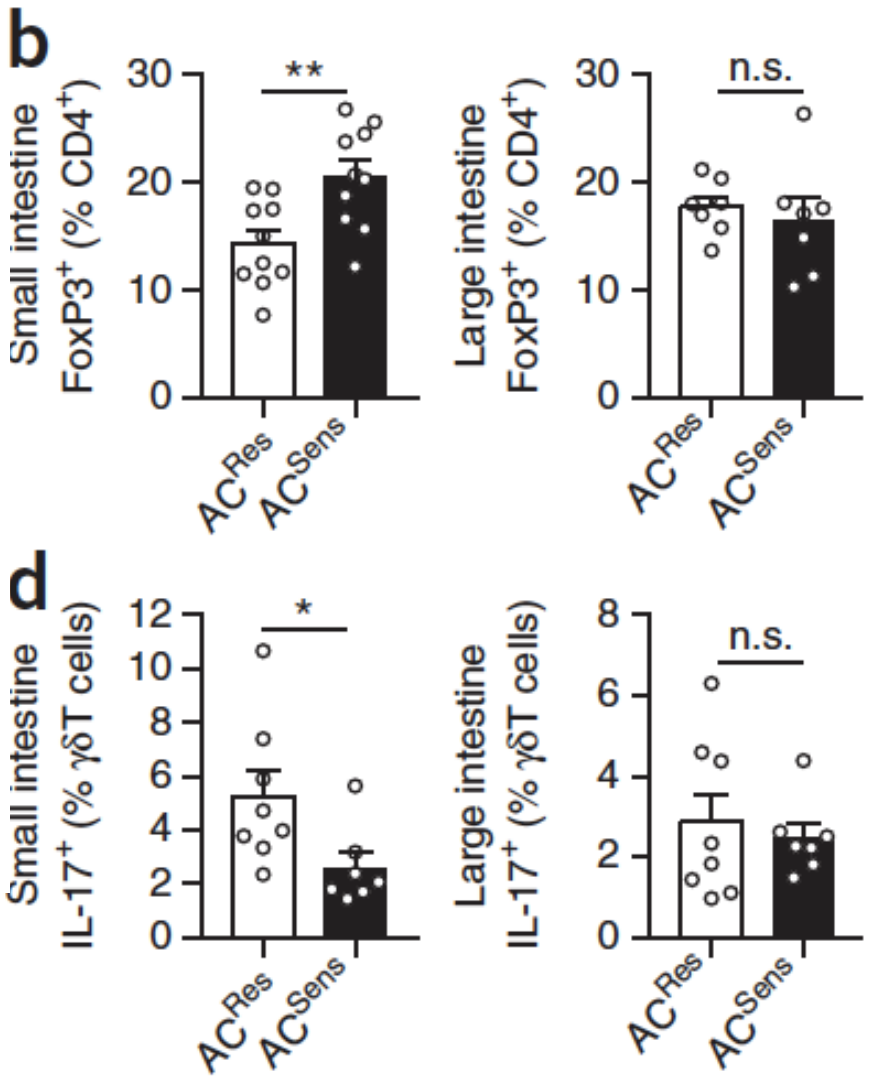
Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells

Corinne Benakis[1,5], David Brea[1,5], Silvia Caballero[2,3], Giuseppe Faraco[1], Jamie Moore[1], Michelle Murphy[1], Giulia Sita[1], Gianfranco Racchumi[1], Lilan Ling[4], Eric G Pamer[2–4], Costantino Iadecola[1] & Josef Anrather[1]

Commensal gut bacteria impact the host immune system and can influence disease processes in several organs, including the brain. However, it remains unclear whether the microbiota has an impact on the outcome of acute brain injury. Here we show that antibiotic-induced alterations in the intestinal flora reduce ischemic brain injury in mice, an effect transmissible by fecal transplants. Intestinal dysbiosis alters immune homeostasis in the small intestine, leading to an increase in regulatory T cells and a reduction in interleukin (IL)-17–positive γδ T cells through altered dendritic cell activity. Dysbiosis suppresses trafficking of effector T cells from the gut to the leptomeninges after stroke. Additionally, IL-10 and IL-17 are required for the neuroprotection afforded by intestinal dysbiosis. The findings reveal a previously unrecognized gut-brain axis and an impact of the intestinal flora and meningeal IL-17^{+} γδ T cells on ischemic injury.

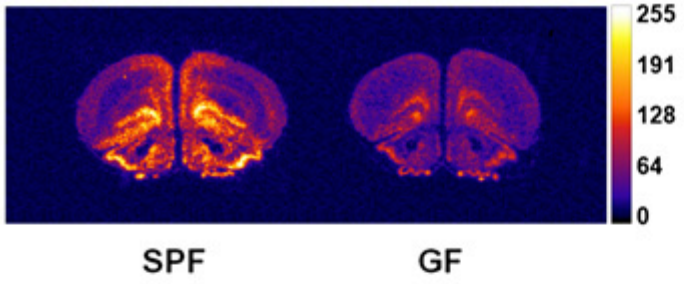
Commensal microbiota affects ischemic stroke outcome

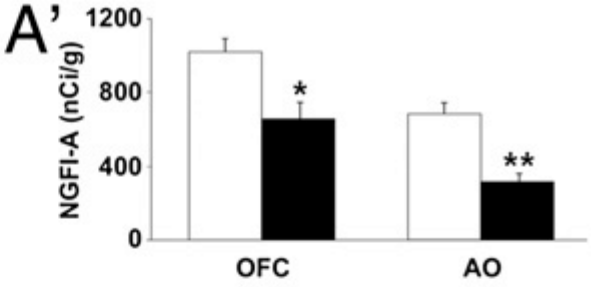


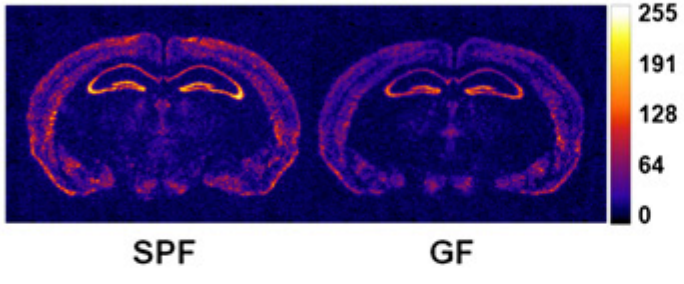


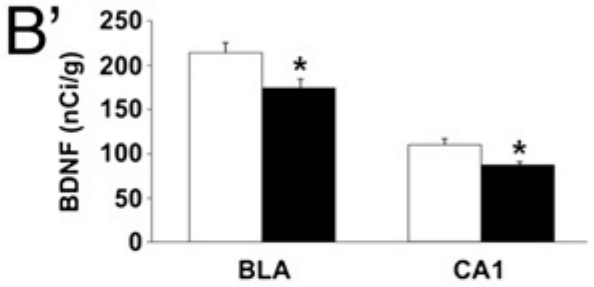
Benakis et al, Nat Med 2016

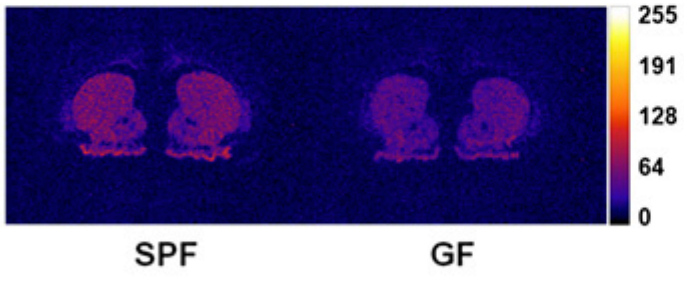
GUT MICROBIOTA, BRAIN DEVELOPMENT

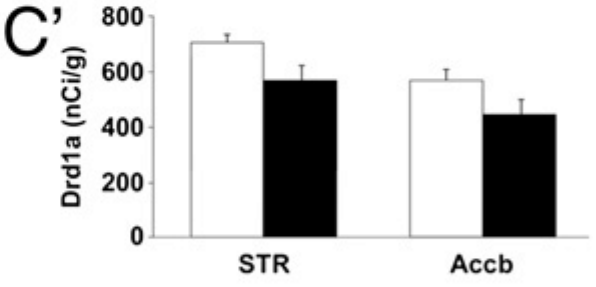


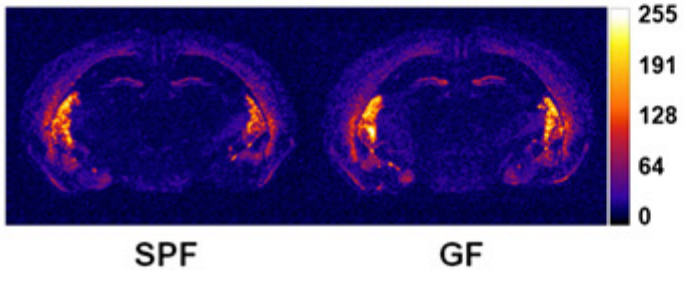


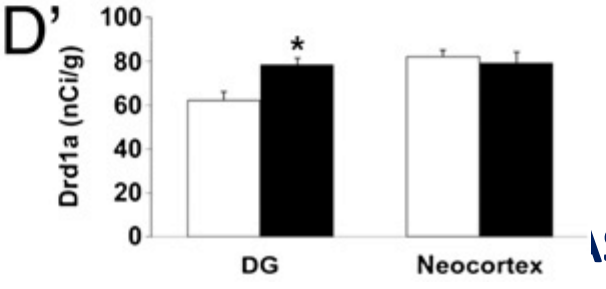












PRIMARY FUNCTIONS OF THE GUT MICROBIOTA

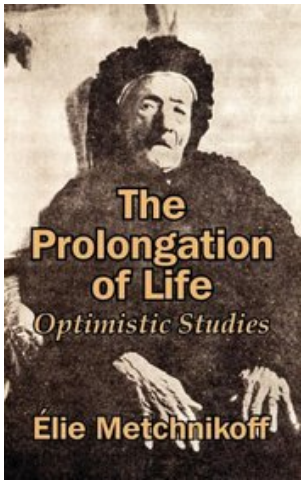
- **Metabolic functions:** fermentation of nondigestible dietary residue and endogenous mucus: salvage of energy as SCFA, production of vitamin K, absorption of ions.

- **Defensive functions:** protection against pathogens (the barrier effect).

- **Trophic functions:** control of epithelial cell proliferation and differentiation; development and homeostasis of the immune system.

Guarner & Malagelada, Lancet 2003

Probiotics



Eli Metchnikoff (1845-1916)

'The Prolongation of Life: Optimistic Studies' (1908)

Probiotics

FAO/WHO definition (2001):

'Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host'

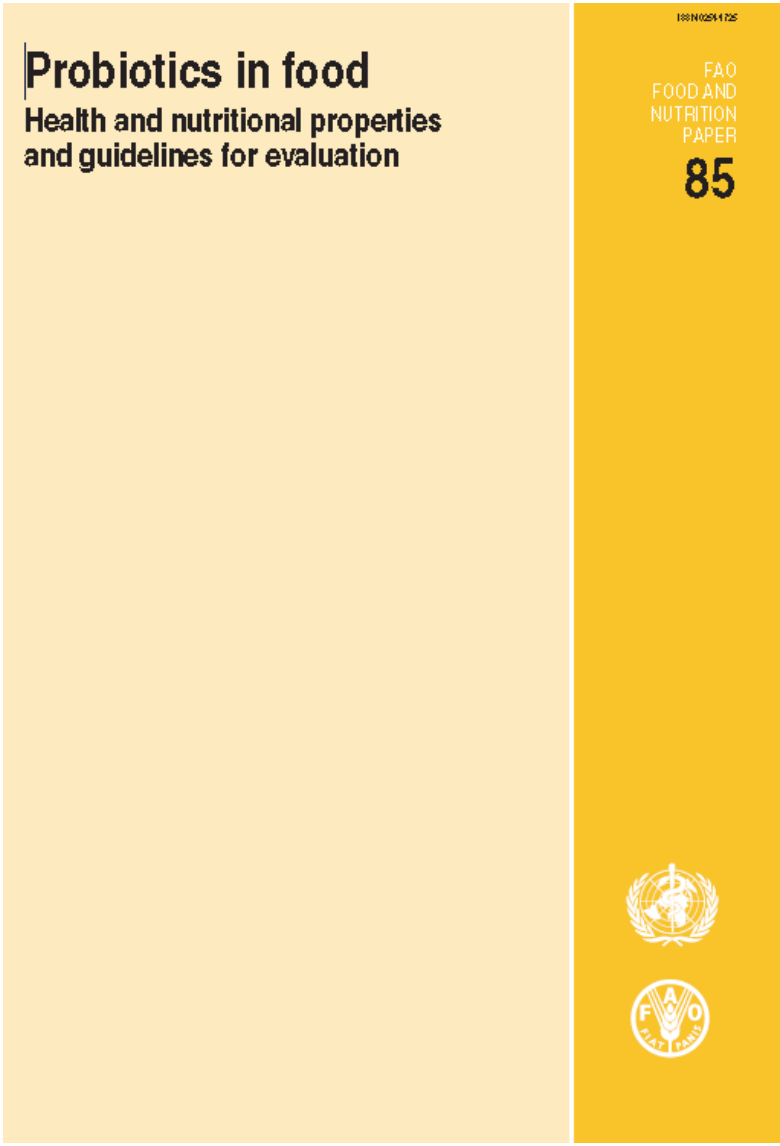
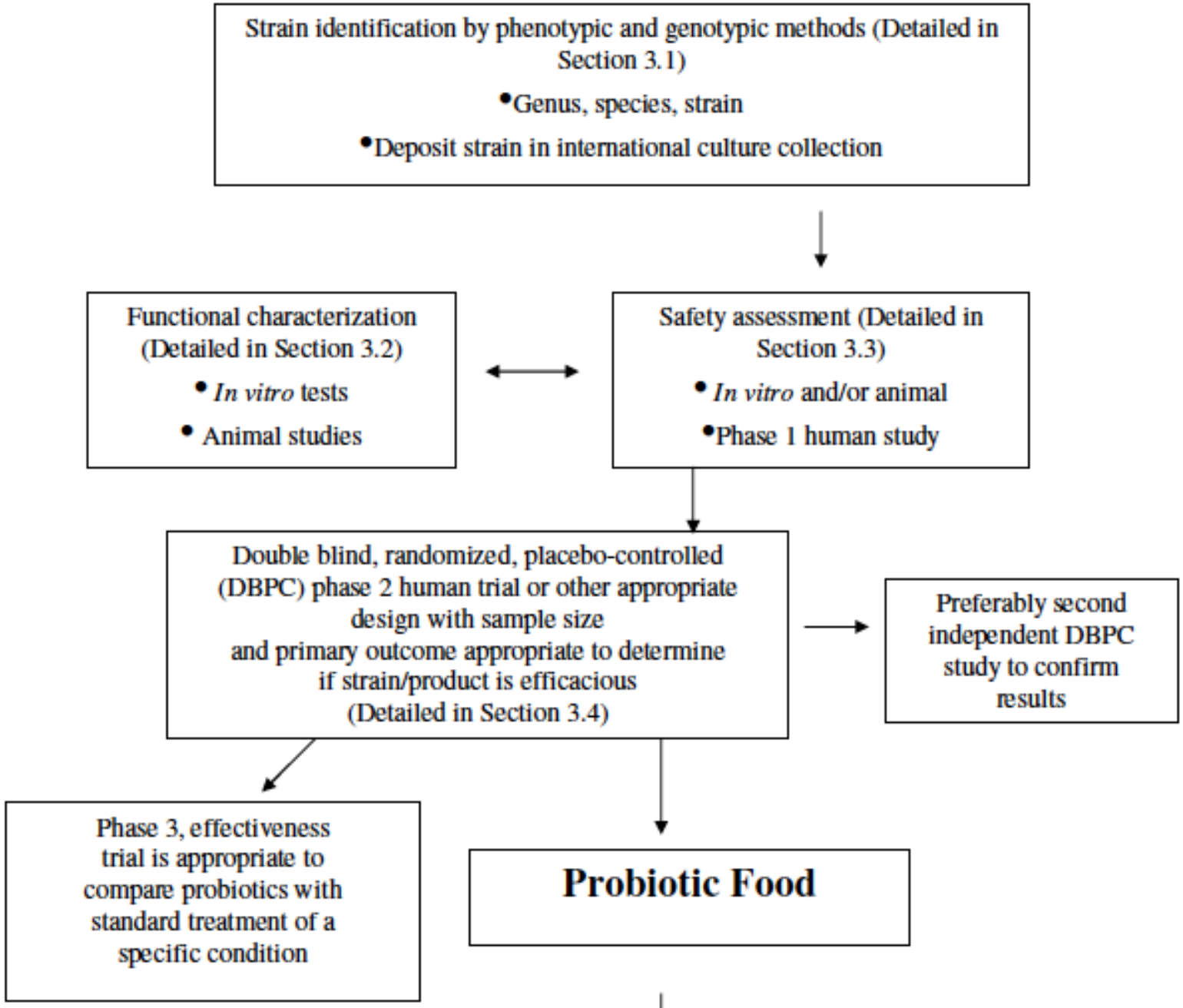
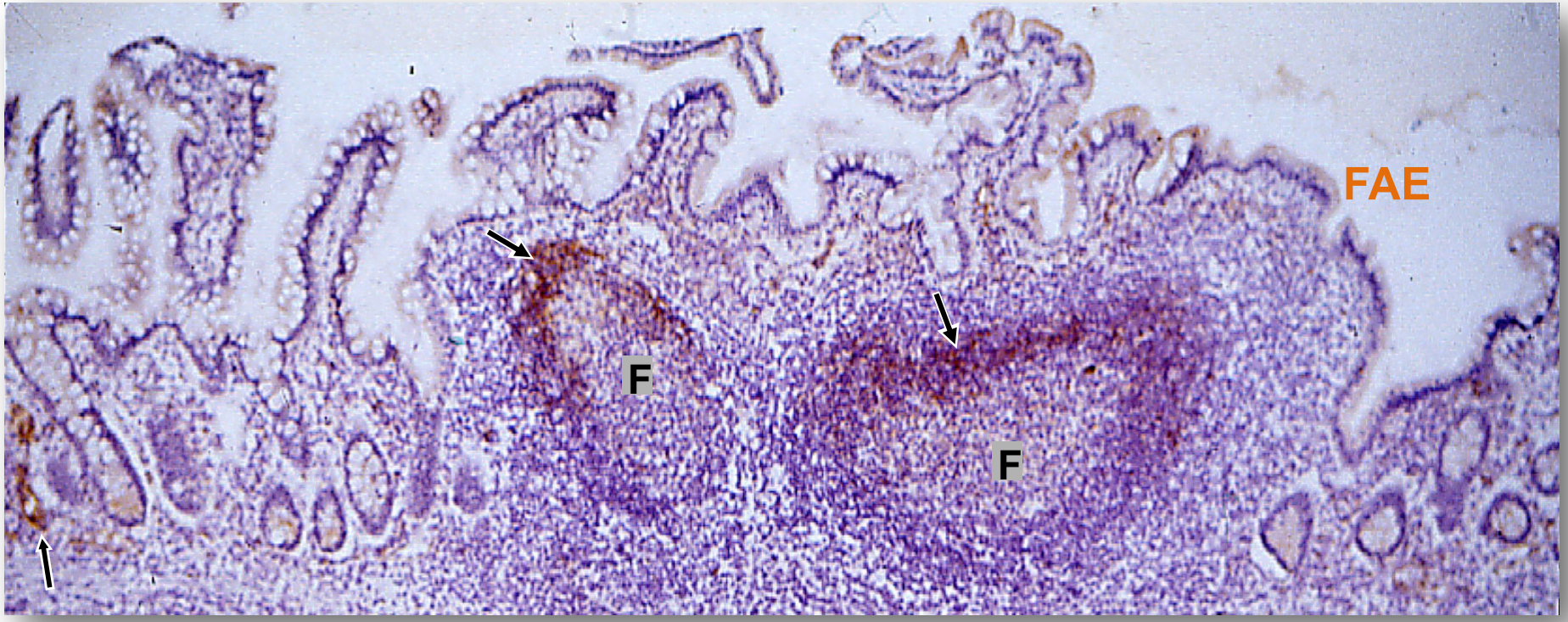


Figure 1. Guidelines for the Evaluation of Probiotics for Food Use



ISSN 0254-4725
FAO FOOD AND NUTRITION PAPER
85

Induction of the Immune System

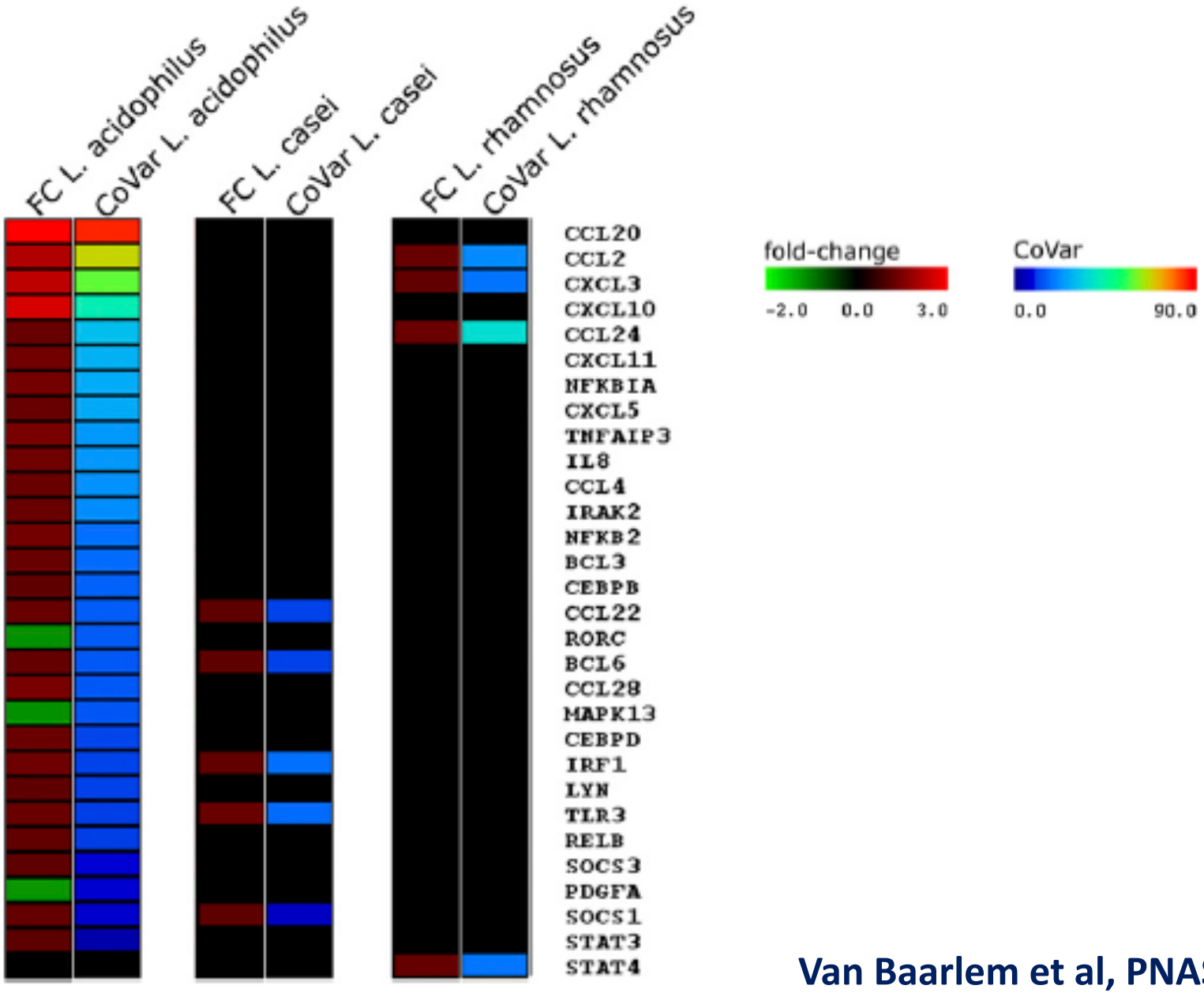


Gut-Associated Lymphoid Tissue structures are strategically situated in relation to the greatest concentration of microbiota

- **Peyer's patches:**
  distal ileum (nos. 100-250)
- **Isolated lymphoid follicles (ILFs):**
  large bowel (nos. ~ 30 000)

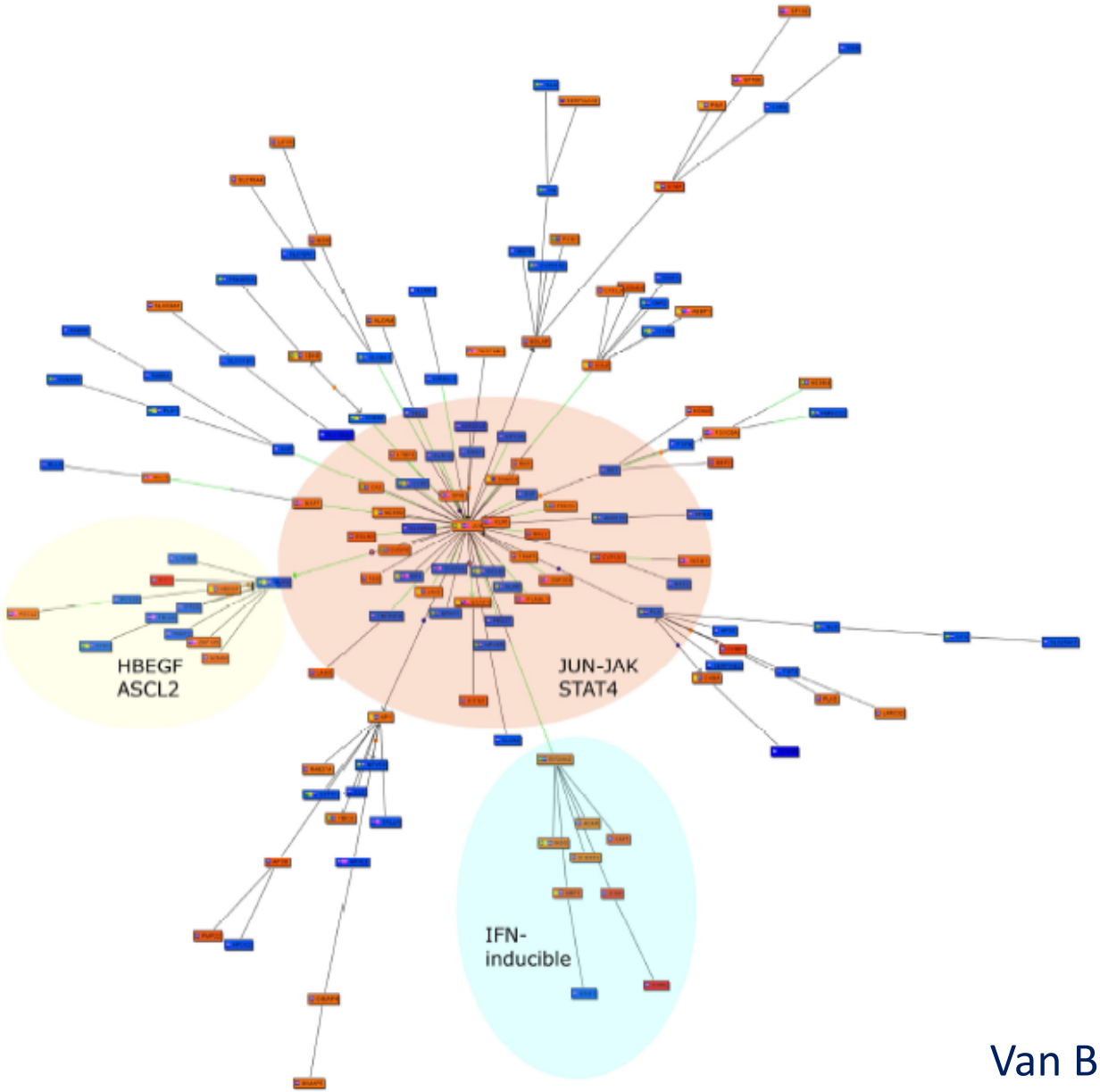
Brandtzaeg, Immunological Investigations 2010

Mucosal responses after consumption of probiotics



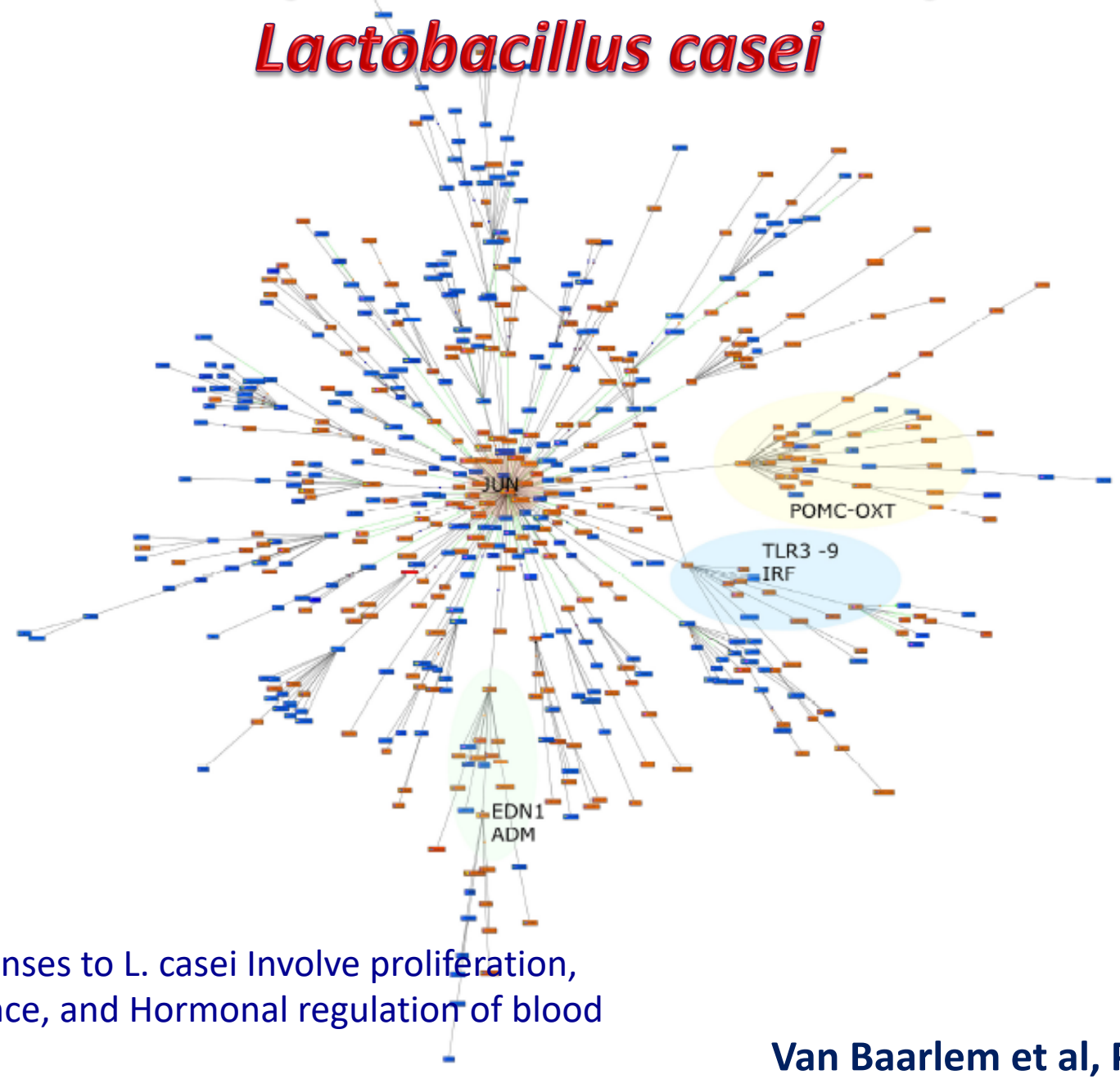
Van Baarlem et al, PNAS 2010

Mucosal responses after consumption of LGG



Van Baarlem et al, PNAS 2010

Mucosal responses after consumption of *Lactobacillus casei*



Mucosal responses to L. casei Involve proliferation, Th1–Th2 Balance, and Hormonal regulation of blood pressure.

Van Baarlem et al, PNAS 2010

A Resource Sensitive Solution

Global Guidelines

- View the Guidelines in Mandarin
- View the Guidelines in Russian
- Acute Diarrhea
- Acute Viral Hepatitis
- Asymptomatic Gallstone Disease
- Celiac Disease
- Colorectal Cancer Screening
- Common GI Symptoms
- Constipation
- Diverticular Disease
- Dysphagia
- Endoscope Disinfection
- Esophageal Varices
- GERD
- Helicobacter Pylori in Developing Countries

Home: Guidelines: Global Guidelines: Probiotics and Prebiotics

Share

WGO Practice Guideline - Probiotics and Prebiotics

Definition: Probiotics are live microbes that can be formulated into many different types of products, including foods, drugs, and dietary supplements. Species of *Lactobacillus* and *Bifidobacterium* are most commonly used as probiotics, but the yeast *Saccharomyces* cerevisiae and some E. coli and Bacillus species are also used as probiotics. Lactic acid bacteria (LAB), including species of *Lactobacillus*, which have been used for preservation of food by fermentation for thousands of years, can serve a dual function by acting as agents of food fermentation and, in addition, potentially imparting health benefits. Strictly speaking, however, the term "probiotic" should be reserved for live microbes that have been shown in controlled human studies to impart a health benefit. Fermentation of food provides characteristic taste profiles and lowers the pH, which prevents contamination by potential pathogens. Fermentation is globally applied in the preservation of a range of raw agricultural materials (cereals, roots, tubers, fruit and vegetables, milk, meat, fish etc.).

Translated Versions

English French Portuguese
Mandarin Russian Spanish

Feedback

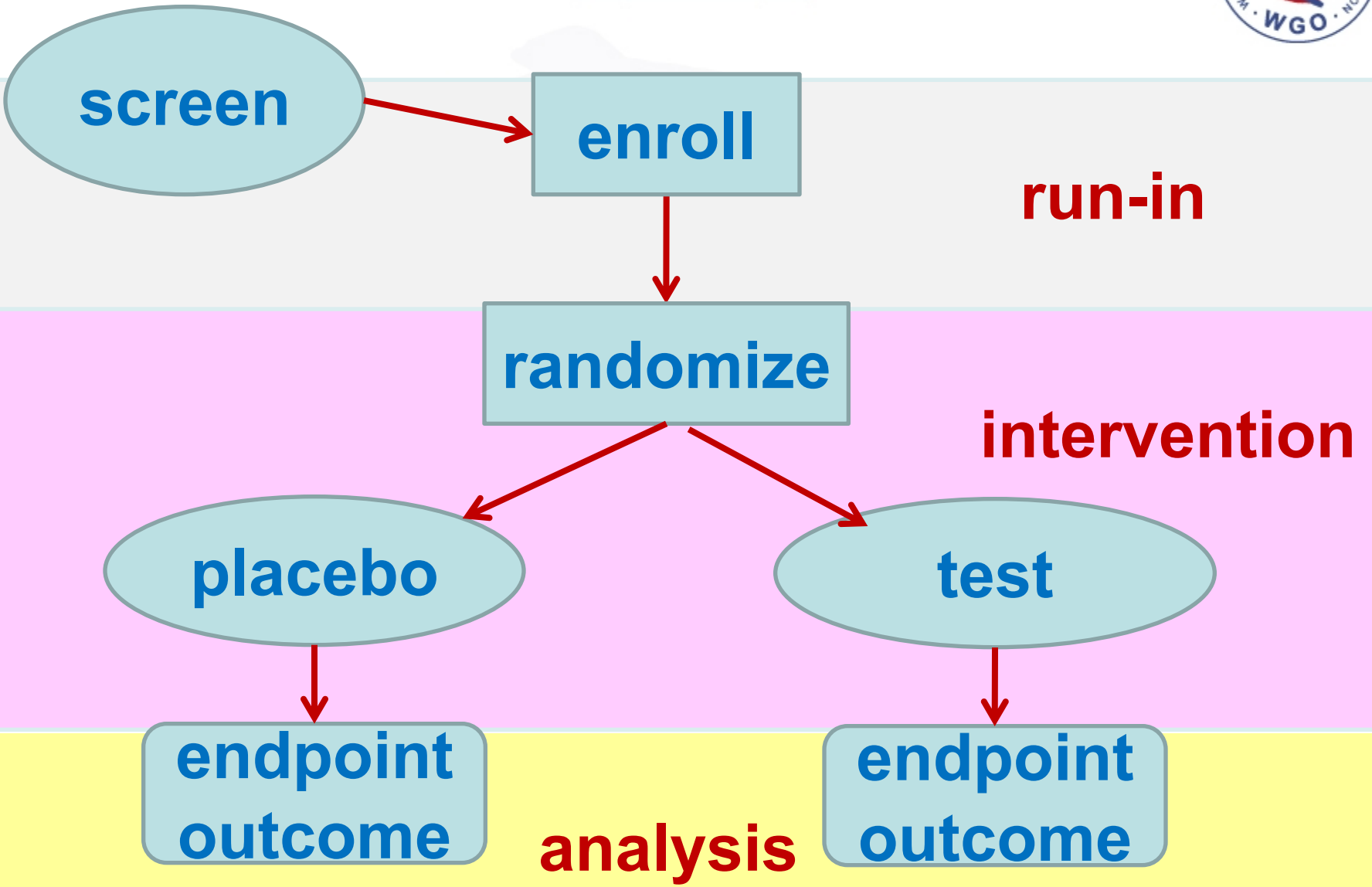
Graded Evidence

- Meta-analyses, Systematic reviews, Practice guidelines
- Clinical Trials

Review Team

- Francisco Guarner (Chair, Spain)

STUDY DESIGN



Probiotics and prebiotics

February 2017

Table 8 Evidence-based *adult* indications for probiotics, prebiotics, and synbiotics in gastroenterology. * Oxford Centre for Evidence-Based Medicine levels of evidence (see Table 7)

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
Diarrhea					
Treatment of acute diarrhea in adults	*Lactobacillus paracasei* B 21060 or *L. rhamnosus* GG	10^9 CFU, twice daily	3	[8]	–
	Saccharomyces boulardii CNCM I-745, strain of *S. cerevisiae*	10^9 CFU/capsule of 250 mg twice daily	2	[9,10]	–
Antibiotic-associated diarrhea	Yogurt with *Lactobacillus casei* DN114, *L. bulgaricus*, and *Streptococcus thermophilus*	$\geq 10^{10}$ CFU daily	1	[11]	Prevention of AAD in various clinical settings (in-patients and outpatients)
	Lactobacillus acidophilus CL1285 and *L. casei* (Bio-K+ CL1285)	$\geq 10^{10}$ CFU daily	1	[11]	
	Lactobacillus rhamnosus GG	10^{10} CFU/capsule twice daily	1	[11]	
	Saccharomyces boulardii CNCM I-745	10^9 CFU/capsule of 250 mg twice daily	1	[11,12]	
	Lactobacillus reuteri DSM 17938	1×10^8 CFU twice daily	3	[13]	Prevention of AAD in hospitalized patients
	Lactobacillus acidophilus NCFM, *L. paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07, *B. lactis* BI-04	1.70^{10} CFU	2	[14]	
	Ecologic® AAD (*Bifidobacterium bifidum* W23, *B. lactis* W18, *B. longum* W51, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W37 and W55, *L. paracasei* W72, *L. plantarum* W62, *L. rhamnosus* W71, and *L. salivarius* W24)	10^9 CFU/g (5 g twice daily)	2	[15]	–
Prevention of *Clostridium difficile*–associated diarrhea (or prevention of recurrence)	*Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R	5×10^{10} CFU daily and $4–10 \times 10^{10}$ CFU daily	2	[16]	–
	Yogurt with *Lactobacillus casei* DN114 and *L. bulgaricus* and *Streptococcus thermophilus*	$10^7–10^8$ CFU twice daily	2	[17]	–

ADULT Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Lactobacillus plantarum 299v (DSM 9843)	5×10^7 billion CFU once daily	2	[40,41]	Improvement in severity of abdominal pain
	Escherichia coli DSM17252	10^9 CFU three times daily	2	[41]	–
	Lactobacillus rhamnosus NCIMB 30174, *L. plantarum* NCIMB 30173, *L. acidophilus* NCIMB 30175, and *Enterococcus faecium* NCIMB 30176.	10 billion bacteria	2	[42]	Improvement in IBS score, mainly in pain and bowel habit score
	Bacillus coagulans and fructo-oligosaccharides	15×10^7, three times daily	2	[43]	Decrease pain, improve constipation
	Lactobacillus animalis subsp. *lactis* BB-12®, *L. acidophilus* LA-5®, *L. delbrueckii* subsp. *bulgaricus* LBY-27, *Streptococcus thermophilus* STY-31	4 billion CFU, twice daily	3	[44]	Improvement in abdominal pain and bloating
	Saccharomyces boulardii CNCM I-745	10^9 CFU/capsule of 250 mg twice daily	2	[45]	Improvement in IBS QOL score
	Bifidobacterium infantis 35624	10^8 CFU, once daily	2	[46,47]	Improvement in subjects global assessment of IBS symptoms
	Bifidobacterium animalis DN-173 010 in fermented milk (with *Streptococcus thermophilus* and *Lactobacillus bulgaricus*)	10^{10} CFU, twice daily	2	[48,49]	Improvement in HRQOL in constipation-predominant IBS
	Lactobacillus acidophilus SDC 2012, 2013	10^{10} CFU, once daily	3	[41,50]	–
	Lactobacillus rhamnosus GG, *L. rhamnosus* LC705, *Propionibacterium freudenreichii* subsp. *shermanii* JS DSM 7067, *Bifidobacterium animalis* subsp. *lactis* Bb12 DSM 15954	10^{10} CFU, once daily	2	[41,51]	–
	Short-chain fructo-oligosaccharides	5 g/daily	3	[52]	–
	Galacto-oligosaccharides	3.5 g/daily	2	[53]	–
	Bacillus coagulans GBI-30, 6086	2×10^9 CFU, once daily	3	[54]	–

Risks of Probiotic Use in Transplant Recipients

Sherid *et al. BMC Gastroenterology* (2016) 16:138
DOI 10.1186/s12876-016-0552-y

BMC Gastroenterology

CASE REPORT Open Access

Liver abscess and bacteremia caused by lactobacillus: role of probiotics? Case report and review of the literature

Table 1 Summary of case reports of liver abscesses due to lactobacilli strains

Reference	Age (years)/Sex	Comorbidities	Predisposing events	Symptoms	Labs	Organism (site)	Treatment	Hospital stay length
Chan (2010) [16]	74/M	DM, HTN, remote history of tonsillar carcinoma	Mirizzi syndrome (common hepatic duct obstruction secondary to external compression by gallstone)	Fever, abdominal pain for 1 day.	Leukocytosis, normal LFTs.	L. rhamnosus (blood, pus, gallbladder)	Percutaneous drainage, cholecystectomy, antibiotics (levofloxacin then both clarithromycin and metronidazole were added)	59 days
Burns (2007) [17]	51/F	None	None	Abdominal pain, vomiting for 2 weeks.	Leukocytosis, elevated LFTs.	L.paracasei (pus)	Percutaneous drainage, antibiotics (meropenem with penicillin and gentamicin, then changed to clindamycin)	53 days
Cukovic-Cavka (2006) [18]	27/M	Crohn's disease	Steroid use	Fever, diarrhea and fatigue.	Leukocytosis.	L.acidophilus (blood, pus)	Percutaneous drainage, antibiotics (ciprofloxacin with metronidazole, then Augmentin with metronidazole)	63 days
Notario (2003)* [15]	73/F	DM	N/A	Fever	N/A	L.rhamnosus (blood, pus)	Surgical drainage, antibiotics (ampicillin with gentamicin)	N/A
Rautio (1999) [19]	74/F	DM, HTN	Heavy dairy consumption.	Fever, abdominal pain for 2 weeks.	Leukocytosis.	L.rhamnosus (pus)	Percutaneous drainage, antibiotics (penicillin, then piperacillin/tazobactam, then ciprofloxacin and clindamycin)	42 days
Larvol (1996)* [14]	39/M	DM, chronic pancreatitis, choledochoduodenostomy	N/A	Fever	N/A	L.acidophilus (blood, pus)	Antibiotics (amoxicillin, gentamicin, augmentin)	N/A
Isobe (1990) [20]	75/M	(HCC, Parkinson's disease	Intratumoral ethanol injection therapy for HCC	Fever	Intrahepatic gas by U/S and CT scan	L.plantarum (blood)	Antibiotics (piperacillin)	52 days (after developing fever)
Sherid (2016) (the current case)	82/F	DM,HTN, ESRD, cholecystectomy	Cholecystectomy, probiotic use	Fever, vomiting	Leukocytosis, elevate LFTs, right pleural effusion	N/A	Percutaneous drainage, antibiotics (imipenem, vancomycin)	19 days

Beneficial Microbes, 2015; 6(1): 3-17

Wageningen Academic Publishers

The administration of probiotics and synbiotics in immune compromised adults: is it safe?

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Received: 16 April 2014 / Accepted: 16 June 2014

RESEARCH ARTICLE

Abstract

This study aimed to systematically evaluate safety of probiotics and synbiotics in immune compromised adults (≥18 years). Safety was analysed using the Common Terminology Clinical Adverse Events (CTCAE version 4.0) classification, thereby providing an update on previous reports using the most recent available clinical data (2008-2013). Safety aspects are represented and related to number of participants per probiotic strain/culture, study duration, dosage, clinical condition and selected afflictions. Analysis of 57 clinical studies indicates that probiotic and/or synbiotic administration in immune compromised adults is safe with regard to the current evaluated probiotic strains, dosages and duration. Individuals were considered immune compromised if HIV-infected, critically ill, underwent surgery or had an organ- or an autoimmune disease. There were no major safety concerns in the study, as none of the serious adverse events (AE)s were related, or suspected to be related, to the probiotic or synbiotic product and the study products were well tolerated. Overall, AEs occurred less frequent in immune compromised subjects receiving probiotics and/or synbiotics compared to the control group. In addition, the results demonstrated a flaw in precise reporting and classification of AE in most studies. Furthermore, generalisability of conclusions are greatly limited by the inconsistent, imprecise and potentially incomplete reporting as well as the variation in probiotic strains, dosages, administration regimes, study populations and reported outcomes. We argue that standardised reporting on adverse events (CTCAE) in 'food' studies should be obligatory, thereby improving reliability of data and re-enforcing the safety profile of probiotics.

Keywords: food safety legislation, immunocompromised people, prebiotics, probiotics, synbiotics

Uso de Probióticos en Pacientes Inmunosuprimidos

- El riesgo de infecciones o bacteremia/fungemia con los probióticos conocidos es bajo, menor de 1 en 4000 ($p<0.00025$).

Fermented Foods reduce risk for Allergic Diseases

TABLE 2 ORs and 95% CIs for Allergic Diseases in Relation to Food and Dietary Habits

Dietary Habit	No. of Responses	Crude OR (95% CI)			
		Eczema, n = 368	Asthma, n = 66	ARC, n = 130	Total Allergy,[d] n = 432
Fermented food[a]	84	0.61 (0.37–1.01)	0.90 (0.35–2.31)	0.52 (0.22–1.21)	0.53 (0.32–0.87)
Food from farm[b]	138	0.78 (0.53–1.15)	0.88 (0.41–1.90)	0.55 (0.29–1.05)	0.67 (0.46–0.98)
Hand dishwashing	126	0.49 (0.32–0.77)	0.21 (0.05–0.85)	0.78 (0.42–1.42)	0.51 (0.34–0.77)
Home cooking[c]					
Never/almost never	72	1	1	1	1
Approximately half the time	533	0.88 (0.53–1.47)	1.67 (0.50–5.55)	0.70 (0.36–1.34)	0.77 (0.47–1.26)
Most of the time/always	414	0.84 (0.51–1.40)	1.60 (0.47–5.44)	0.55 (0.28–1.09)	0.72 (0.44–1.19)
Breastfeeding duration, mo					
0–4	145	1	1	1	1
>4–8	373	0.92 (0.62–1.36)	0.70 (0.34–1.41)	0.86 (0.49–1.51)	0.87 (0.59–1.28)
≥8	430	0.94 (0.64–1.39)	0.65 (0.33–1.31)	0.99 (0.58–1.72)	0.90 (0.61–1.31)

[a] Question: "Does the child eat food that includes fermented vegetables (such as sauerkraut or fermented cucumber) or other fermented foodstuffs?" Responses: never/almost never; at least once a month.

[b] Question: "Do you sometimes buy hens' eggs, meat, or unpasteurized milk directly from a farm?" Responses: yes; no.

[c] Question: "During the child's first year of life, how often was he/she given home-cooked food?" Responses: never/almost never; approximately half the time; most of the time/always.

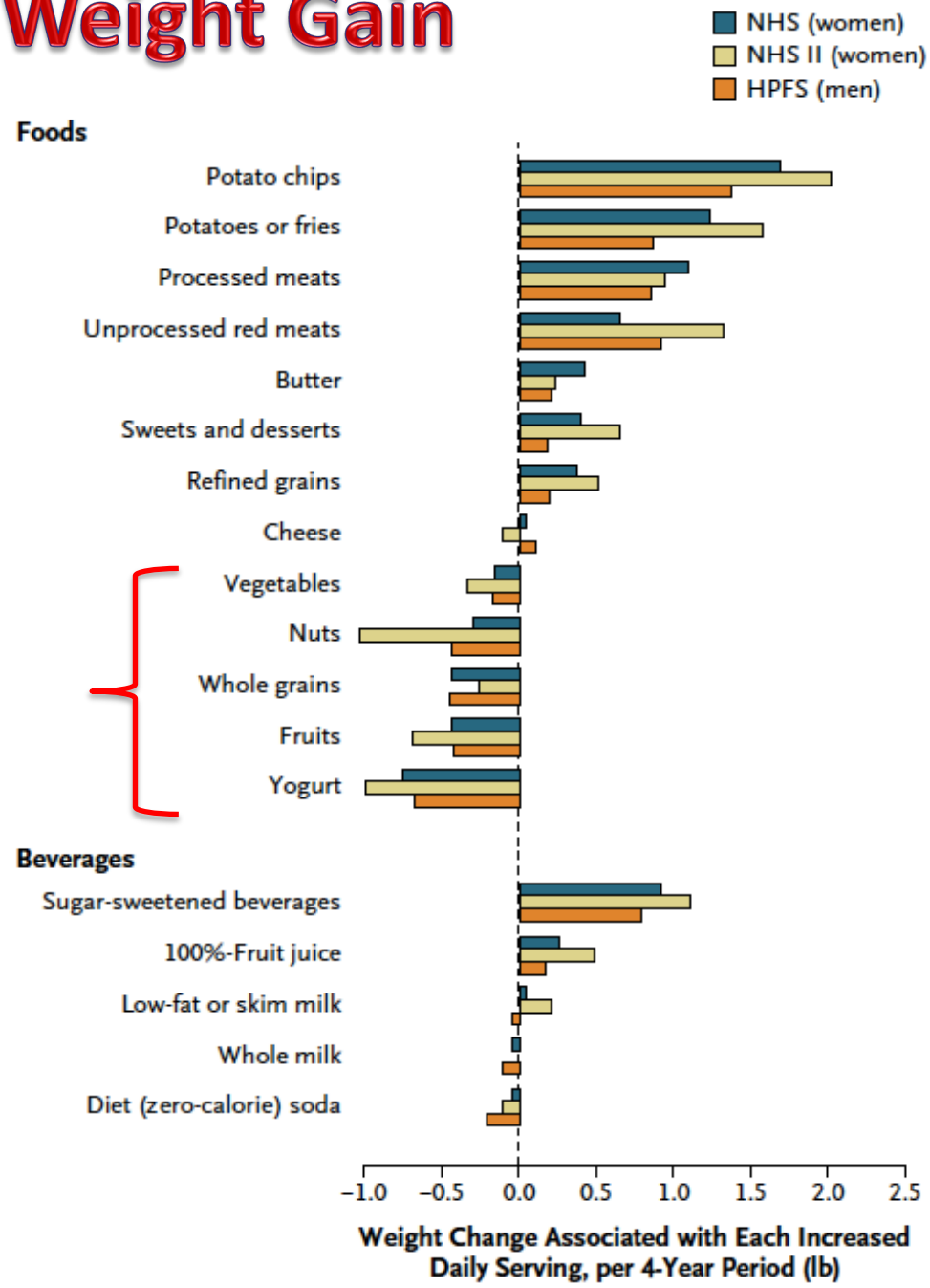
[d] Any of eczema, asthma, or ARC.

Hesselmar et al, Pediatrics 2015

Diet and Long-Term Weight Gain

- Prospective observational study involving three separate cohorts that included 120,877 women and men who were free of chronic diseases and not obese at baseline.
- Follow-up period from 1986 to 2006.

Feeding the gut microbiota proved very beneficial!



Mozaffarian et al, NEJM 2011

ISAPP consensus statement

Summary of conclusions

- Retain the FAO/WHO definition for probiotics, with a minor grammatical correction as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”
- Keep live cultures, traditionally associated with fermented foods and for which there is no evidence of a health benefit, outside the probiotic framework

LIVE ACTIVE

- Allow the term ‘probiotics’ for microbial **species** that have been shown in properly controlled studies to confer benefits to health

PROBIOTIC

- Any specific health claim beyond “contains probiotics” must be further substantiated

PROBIOTIC HEALTH CLAIM

- Keep undefined, faecal microbiota transplants outside the probiotic framework
- New commensals and consortia comprising defined strains from human samples, with adequate evidence of safety and efficacy, can be termed ‘probiotics’

Hill et al, Nature Rev Gastroenterology & Hepatology 2014