International Yakult Symposium 2022

Microbiota and Probiotics: Chances and Challenges!

13th – 14th October 2022
Museo Nazionale Scienza e Tecnologia
Leonardo da Vinci
Milan, Italy

Yakult
Science for Health

Scientific Committee

Prof. Mauro Serafini
University of Teramo, Italy

Emeritus Prof. Michael Gleeson
Loughborough University, UK

Dr. Bruno Pot
Yakult Europe, The Netherlands

Prof. Patrizia Brigidi
University of Bologna, Italy

Dr. Arianna Rolandi
Yakult Italia, Italy

Conference Venue

Museo Nazionale Scienza e Tecnologia Leonardo da Vinci
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Preface

In 2018 Yakult Group in Europe held our last International Yakult Symposium (IYS). While 2020 would have been the year where we would have celebrated the 10th edition of this IYS series, the corona virus decided otherwise.

Now four years later, it is with great pleasure to welcome you to this 10th IYS edition, in the wonderful city of Milan.

We have chosen the title “Microbiota and Probiotics: Chances and Challenges!” for this symposium, as research in the field of the gut microbiota is progressing at an ever increasing speed, yielding results that support the enormous potential of microbiota driven interventions with pre- and probiotics, but, as always in science, with new knowledge raising new questions, new challenges.

During this **10th International Yakult Symposium** we will turn the spectacular National Science Museum Leonardo da Vinci into a learning and discussion platform, where different aspects of probiotics and microbiota within gut health will be explored: from longevity to gut brain axis, passing through microbiome diversity. In a beautiful historical setting that is honouring incredible scientific developments from the past, we intend to discuss the science of the future: how new gut microbiome insights can help us continue to pioneer efficient and safe interventions, or how to overcome the remaining questions related to probiotic modes of action, interindividual variation, or changes of the microbiota at old age…

We look really forward to welcoming you in Milan to fuel the discussion and present your own research poster!

See you on October 13 and 14!

Yakult Europe B.V.
Yakult Italia SrL
All European Yakult science members

Scientific Programme

Thursday 13th October

10:00 **Open registration and poster assembly**

10:00 **Museum guided tour (optional)**

12:00 **Lunch**

12:45 **OPENING AND WELCOME WORDS**
Mr. Hiroyasu Matsubara, Managing Director, Yakult Europe
Mr. Yuji Amamiya, Consul General of Japan in Milan
Mr. Fiorenzo Galli, General Director Museo Nazionale Scienza e Tecnologia

13:00 **KEY NOTE LECTURE I**
The crewed journey to space and its implications for the human microbiome
Prof. Christine Moissl-Eichinger, Medical University of Graz, Austria

13:40 **SESSION 1. GUT-BRAIN AXIS AND STRESS, ONE OF A KIND?**
Chair: Prof. Robert-Jan Brummer, Örebro University, Sweden
CHANCES
13:45 **Parkinson's Disease – no Guts no Glory – the potential of food-based therapies**
Prof. Aletta Kraneveld, Utrecht University, The Netherlands
14:15 **IBS: is it all between the ears?**
Prof. Francisco Guarner, Teknon Medical Centre, Spain
14:45 **How microbes affect depression: underlying mechanisms via the gut-brain axis and the modulating role of probiotics**
Dr. Kazunori Matsuda, Yakult Central Institute, Japan
CHALLENGES
15:15 **Overcoming the brain barrier: a challenge for bacteria?**
Prof. Roosmarijn Vandenbroucke, Flanders Institute for Biotechnology, Belgium

15:45 **Tea & coffee break / Poster viewing**

16:15 **SESSION 2. DIVERSITY AND RESILIENCE**
Chair: Dr. Gwen Falony, KU Leuven, Belgium
CHANCES
16:20 **Gut microbial diversity: one health and probiotics**
Dr. Olaf Larsen, Vrije Universiteit Amsterdam, The Netherlands
16:50 **Opportunities relating to fermented fFoods**
Prof. Paul Cotter, Teagasc Food Research Centre and APC Microbiome Ireland, Ireland
CHALLENGES
17:20 **Development of the infant microbiota: from bifido-dominated to a diversity and resilient ecosystem**
Prof. Christoph Lacroix, Institute of Food Science and Nutrition at the ETH Zurich, Switzerland

17:50 **Tea & coffee break**

18:10 **SESSION 3. FLASH TALKS FROM POSTERS**
Chair: Prof. Mauro Serafini, University of Teramo, Italy
Six abstracts selected by the Scientific Committee (5 min each)

19:00 **End of sessions**

19:00 **Museum guided tour (optional)**

20:00 **Pre-dinner drinks** at the Museum, Sala Biancamano

20:30 **Dinner** at the Museum, Spazio Polene
Welcome address: Dr. Mauro Bonati, Managing Director, Yakult Italia

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Friday 14th October

08:30 **KEY NOTE LECTURE II**
Safety of microorganisms used as probiotics: which strategies for risk assessment?
Prof. Pier-Sandro Cocconcelli, Catholic University of the Sacred Heart, Italy

09:10 **SESSION 4. PROBIOTICS FROM PHARMA TO FOOD**
Chair: Prof. Fabio Pace, Ospedale "Bolognini" Seriate (BG), Italy
CHANCES
09:15 **Living foods: a safe salvation for health**
Prof. Lorenzo Morelli, Catholic University of the Sacred Heart, Italy
09:45 **Living drugs: a solution with many benefits**
Prof. Stephan Bischoff, University of Hohenheim, Germany
CHALLENGES
10:15 **The importance of the responder / non-responder issue for clinical trials with probiotics. Is the traditional RCT design adequate?**
Prof. Robert-Jan Brummer, Örebro University, Sweden

10:45 **Tea & coffee break / Poster viewing**

11:15 **SESSION 5. HEALTHY AGEING: MYTH OR HOPE?**
Chair: Prof. André Bachi, Santo Amaro University, Brazil
CHANCES
11:20 **Microbiota composition from 1 till 100**
Prof. Gaspar Pérez Martínez, Institute of Agrochemistry and Food Technology (CSIC), Spain
11:50 **Gut microbiota changes in the extreme decades of human life: a focus on centenarians**
Prof. Patrizia Brigidi, University of Bologna, Italy
CHALLENGES
12:20 **Probiotics and the ageing immune system**
Dr. Caroline Childs, University of Southampton, UK

12:50 **Poster Prize awards**
Chair: Emeritus Prof. Michael Gleeson, Loughborough University, UK

13:10 **Closing**
Dr. Bruno Pot, Science Director, Yakult Europe

13:15 **Lunch**

14:30 **End of International Yakult Symposium**

Scientific committee

Prof. Mauro Serafini, University of Teramo, Italy

Professor Serafini is Full Professor of Human Nutrition and Head of the Functional Foods and Metabolic Stress Prevention Laboratory at Teramo University where he teaches Human Nutrition, Nutritional Sustainability and Experimental Nutrition. He is visiting Professor at the faculty of Food Technology and Biotechnology of Zagreb University where teaches "Food, Nutrition and Health".

He obtained his degree in Nutrition in 1992, and his PhD in Experimental Physiopathology in 2001, at Pavia University. He spent two years as postdoc at the Nutritional Immunology Lab at HNRC at Tufts University. He was Senior Fellow at Kyoto medical University, department of inflammation. Serafini has been included by Thomson Reuters in the list of international researchers displaying the greatest numbers Highly Cited Papers, top 1% most cited for ten years. He is Chief Editor of Frontiers in Nutritional Epidemiology, Associate Editor of Nutrition and Aging, Frontiers in Nutritional Immunology and Frontiers in Sustainable Diets. He received by the Council of Italian "Foreign Press" the "Gusto Award" for the best communication in nutrition. Recently Prof. Serafini received the title of Knight Commander of the Italian Republic for scientific merit."

Prof. Patrizia Brigidi, The University of Bologna, Italy

Department of Medical and Surgical Sciences, Alma Mater Studiorum-Università di Bologna, Via Massarenti, 9. 40126 Bologna, Italy
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Patrizia Brigidi is Full Professor of "Fermentation Biotechnology" at the Department of Medical and Surgical Sciences of the University of Bologna. She is Member of the Presidency Council of the National Technological Cluster A.Food and Expert in the Italian Delegation in Horizon Europe Programming Committee, Cluster VI. Her research activity is documented by over 250 papers on peer-reviewed international journals, focused on the study of human microbiome, in the perspective of its modulation to promote the host's health. She leads and participates a number of European and National projects aimed at studying, by omics approaches, the role of microbiome in healthy aging and non-communicable diseases.

Emeritus Prof. Michael Gleeson, Loughborough University, UK

Michael is Emeritus Professor of Exercise Biochemistry at Loughborough University. He retired in 2016 after 40 years of research and teaching mostly related to the diet, metabolism, health and performance of athletes. He had a particular interest in the effects of diet and exercise on the function of the immune system and is a Past-President of the International Society of Exercise and Immunology (ISEI). He has provided advice on minimising risks of infection and nutritional strategies to maintain immune function and optimise performance to numerous sports clubs and organisations. He has published several books on exercise biochemistry, sport nutrition, exercise immunology and healthy lifestyle behaviours as well as over 200 research papers in scientific and medical journals. He is still an active science writer and in the past few years has contributed to international expert consensus reviews sponsored by the IOC, ISEI, ISSN and UEFA. He is also a nutrition consultant to Leicester City FC, a co-author of the recent UEFA expert group statement on nutrition in elite football (Collins et al. 2021) and author of the book entitled Nutrition for Top Performance in Football (Meyer & Meyer Sport 2022).

Dr. Arianna Rolandi, Yakult Italia, Italy

Science and Corporate Communication Head at Yakult Italia since 2007. I manage a talented team of women, sharing with them a passion for science and innovation. We work constantly to disseminate the values of scientific research and to carry out educational projects on healthy lifestyles and proper diet.

My professional experience starts in Pharma Industries as a Medical Marketing Manager in different therapeutic areas as psychiatry, neurology, geriatric, gynaecology, infectiology, gastroenterology and evolved as Head of Corporate Communication. After which I held the position of Director of the Healthcare Department at Hill&Knowlton, a global public-relations company (WPP Group). I also worked as a strategic and crisis management consultant in health & wellness Industry and in a leading Italian public hospital.

Dr. Bruno Pot, Yakult Europe, The Netherlands

Science Director at Yakult Europe, Guest Professor at the Vrije Universiteit Brussels, PRI president

Bruno Pot graduated at the University of Gent, Belgium. In subsequent postdocs he performed research on lactic acid bacteria. In 1997 he joined the company Yakult as science manager Benelux. Between 2001–2016 he worked as Research Director at the Institut Pasteur in Lille and as Director Business Development at the bioinformatics company Applied Maths. Until today he is Guest Professor at the Vrije Universiteit Brussel. Since 2016 Bruno is back with Yakult as Science Director Europe. He is member of the Taxonomic Subcommittee for Lactobacillus and Bifidobacterium, President of the Pharmabiotic Research Institute, and board member of ILSI-EU and LABIP.

Chairs

Prof. Robert JM Brummer, Örebro University, Sweden

Robert-JM Brummer studied medicine at Nijmegen University, the Netherlands and performed his PhD studies in Göteborg, Sweden (PhD 1992) and continued clinical training in internal medicine and gastroenterology at University Hospital Maastricht, the Netherlands. He became professor at Maastricht University 2002 and was acting director of the nutrition research institute (NUTRIM) of the University. Subsequently, he became research director at the "Wageningen Centre for Food Science", later "TI Food and Nutrition", the Netherlands.

From 2008 he joined Örebro University, Sweden as professor of Gastroenterology and Clinical Nutrition and senior consultant at the University Hospital. Brummer was Dean of the Faculty of Medicine and Health during 6 years and currently is Pro-Vice-Chancellor of the University. In that role he also is director of the Örebro University Food & Health Programme. He leads both the interdisciplinary "Nutrition-Gut-Brain Interactions Research Centre" at the University as well as the recently governmentally funded national research excellence centre "Plant-based Proteins for Health and Wellbeing – PAN Sweden". Furthermore, he is engaged in national boards and strategies regarding food and nutrition research and innovation and acts as reviewer for several international research councils and represents Sweden in the European Universities Association expert group on innovation.

His main field of interest in research is the nutrition/microbe-gut-brain interactions with special reference to human application and still performs all research endoscopic investigations himself.

Dr. Gwen Falony, KU Leuven, Belgium

Gwen Falony received his PhD in 2009 from the Vrije Universiteit Brussel (VUB, Belgium), where he studied cross-feeding interactions between bifidobacteria and colon butyrate producers. As a postdoc in the Raes Lab (VUB-KU Leuven, Belgium), he contributed to the development of bioinformatics tools facilitating functional analysis and interpretation of metagenomic data. Later on, as a staff scientist working at the Flemish Institute for Biotechnology (VIB, Belgium), his work focused on defining the boundaries of a health-associated gut microbiota.

He is one of the architects of the Flemish Gut Flora Project (FGFP). He identified transit time as a main contributor to microbiota variation and described a dysbiotic microbiome configuration with high prevalence among individuals suffering from a broad range of inflammation-associated conditions. More recently, his research targets modulation of the colon microbiota away from this potentially deleterious Bact2 enterotype through dietary interventions, drug repurposing, and fecal microbiota transplantation.

Prof. Fabio Pace, Ospedale ''Bolognini'' Seriate (BG), Italy

Prof. Dr. Fabio Pace Graduated in Medicine and Surgery in 1979 at the University of Palermo, where he also specialized in Diseases of the digestive system. In the eighties and nineties Prof. Pace worked as a hospital assistant, and subsequently first level manager at the division and chair of Gastroenterology of the "L. Sacco" University Hospital in Milan (director Prof. G. Bianchi Porro). From 2006 to 2015 Dr. Pace was active as a university researcher at the Department of Biomedical and Clinical Sciences at "L. Sacco" - Milan. Since March 2010, he is director of the complex operating unit of Gastroenterology at the "Bolognini" Hospital in Seriate (BG).

Dr. Pace's research interests are in the field of gastroesophageal reflux disease (GERD), digestive motility disorders, functional pathology in gastroenterology, endoscopy and psycho-gastroenterology valorized with over 240 publications and 14 books on gastroenterology.

Dr. Pace is a member of various scientific societies (Sige, Eage, Gismad) and referee for various international journals in the field of Gastroenterology (Digestive and Liver Disease, Scandinavian Journal of Gastroenterology, Gut, Gastroenterology, Drugs, Drug Development Research, Nature Clinical Practice Gastroenterology & Hepatology, Journal of Cellular and Molecular Medicine).
Prof. Pace is currently Aggregate professor at Milan University, Director of the Gastroenterology Unit - "Bolognini" Hospital of Seriate (BG) and also former Research assistant in Zurich (CH) and Johannesburg (SA).

Prof. Andre Luis Lacerda Bachi, Santo Amaro University, Brazil

Prof. Dr. Andre Luis Lacerda Bachi has a degree in Biological Sciences from the Methodist University of São Paulo (2001), in addition to a Master's (2004) and PhD (2009) in Health Sciences from the Graduate Program in Microbiology and Immunology of the Federal University of São Paulo (UNIFESP). Dr. Bachi is a postgraduate Professor at Santo Amaro University (UNISA), São Paulo, Brazil, and a Visiting Professor at UNIFESP, developing research projects in the area of basic and clinical immunology, e.g. related to the effects of regular physical exercise important in the prevention of upper airway diseases, in athletes as well as in the elderly. These studies, both using experimental models as well as clinical studies, investigate, amongst others, the effect of food supplements that are thought to modulate immune/inflammatory responses, such as glutamine, omega-3 and omega-6 fatty acids, and probiotics.

Dr. Bachi's main interest is in the mechanisms of immune/inflammatory responses, with an emphasis on a better understanding of the roles of cells and molecules produced after the activation of the immune system (antibodies, pro- or anti-inflammatory cytokines, regulatory cytokines, oxidative metabolism, with e.g. the role of low-weight lipoprotein (LDL) oxidation and antioxidant mechanisms).

Oral Presentations

THE CREWED JOURNEY TO SPACE AND ITS IMPLICATIONS FOR THE HUMAN MICROBIOME

Christine Moissl-Eichinger
Medizinische Universität Graz, Austria

Crewed space flight to Mars is planned for the next decade. In preparation for this unparalleled undertaking, a plethora of challenges must be overcome before the actual journey to Mars. The success of the mission will depend on the health of the crew and their ability to work. Therefore, the journey to Mars will also depend on the microbiome and its far-reaching effects on the health of individual crew members, the integrity of the spacecraft, and the food supply. Because humans depend on their microbiome, these microbes are essential and should be managed so that their positive effects outweigh any potential risks. To adequately prepare for a long-term spaceflight to Mars, similar conditions must be thoroughly studied, including the International Space Station (ISS) or other simulation missions where the crew lives in isolation for extended periods of time. In the last years, we have analyzed microbial dynamics in ground-based simulation missions (e.g. HI-SEAS IV[2], Mars 500[4]), but also in real space missions (ISS[3]). Although the microbial community is confined and isolated in these encapsulated systems, it has been shown to be very dynamic and extensive exchanges between the abiotic surface and the human microbiome have been detected. We show that microbial communities on the ISS are very similar to those in closed indoor environments on the ground and are subject to fluctuations, although a core microbiome persists across time and place. The genomic and physiological traits selected by ISS conditions do not appear to be directly relevant to human health, although adaptations toward biofilm formation and surface interactions have been observed. Our results do not raise direct concern for crew health, but suggest a potential threat to material integrity in humid environments.

In a recent publication[1], we summarize all that is known about human spaceflight and its impact on the human microbiome, and provide detailed recommendations for microbial monitoring during all phases of flight, in order to ensure crew safety and health during a long journey to Mars and back.

1. Kuehnast, T., Abbott, C., Pausan, M.R., Pearce, D.A., Moissl-Eichinger, C. and Mahnert, A., 2022. The crewed journey to Mars and its implications for the human microbiome. Microbiome, 10(1), pp.1-14.
2. Mahnert, A., Verseux, C., Schwendner, P., Koskinen, K., Kumpitsch, C., Blohs, M., Wink, L., Brunner, D., Goessler, T., Billi, D. and Moissl-Eichinger, C., 2021. Microbiome dynamics during the HI-SEAS IV mission, and implications for future crewed missions beyond Earth. Microbiome, 9(1), pp.1-21.
3. Mora, M., Wink, L., Kögler, I., Mahnert, A., Rettberg, P., Schwendner, P., Demets, R., Cockell, C., Alekhova, T., Klingl, A. and Krause, R., 2019. Space Station conditions are selective but do not alter microbial characteristics relevant to human health. Nature communications, 10(1), pp.1-18.
4. Schwendner, P., Mahnert, A., Koskinen, K., Moissl-Eichinger, C., Barczyk, S., Wirth, R., Berg, G. and Rettberg, P., 2017. Preparing for the crewed Mars journey: microbiota dynamics in the confined Mars500 habitat during simulated Mars flight and landing. Microbiome, 5(1), pp.1-23.

Prof. Christine Moissl-Eichinger
I received my Dr. rer. nat. from the University of Regensburg, Germany in 2005. Subsequently I worked as a PostDoc at the University clinics in Regensburg (rheumatology) and joined afterwards (2005-2006) the CALTECH/ NASA Jet Propulsion Laboratory in California, US. I returned as a junior group leader to the University of Regensburg (Dept. Microbiology and Archaea Center). In 2014, I accepted an offer from the Medical University of Graz as university professor on “Interactive Microbiome Research”, where I am heading a large research group, acting as speaker for the research field “Microbiome and Infection” and coordinating the extension study program “Medical Research”. My research focuses on Archaea in the human body and special indoor environments, such as the international space station.
Full details on publications, presentations and projects can be found here: https://forschung.medunigraz.at/fodok/suchen.person_uebersicht?sprache_in=en&ansicht_in=&menue_id_in=101&id_in=2006816

PARKINSON'S DISEASE - NO GUTS NO GLORY - THE POTENTIAL OF FOOD-BASED THERAPIES

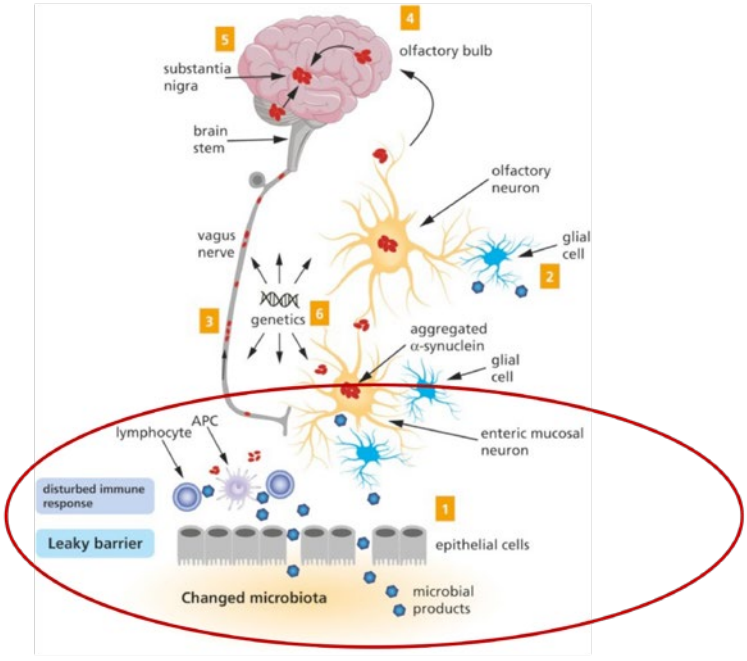
Aletta D. Kraneveld
Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, The Netherlands

Parkinson's disease is the second most common neurodegenerative disease in the world. Hallmark of the disease is the loss of dopaminergic neurons in the substantia nigra and α-synucleinopathology resulting in characteristic motor impairments. Besides the well-known motor deficits Parkinson's patients often suffer from non-motor symptoms, most commonly gastrointestinal dysfunction. The gastrointestinal problems can occur many years before the onset of the motor symptoms of Parkinson's disease.

The reported changes in the composition of the microbiota associated with the accumulation of α-synuclein in the enteric nervous system, leaky gut, and intestinal inflammation in patients point to the relevance of gut-microbiome-immune system-brain axis in Parkinson's disease and support the Braak hypothesis. The Braak hypothesis postulates that an unknown microbial trigger in the gut can be the initiation factor by triggering local neuronal aggregation of α-synuclein that in turn in a prion–like way can spread to the brain (figure). Based on (pre)clinical data the talk will shed light on the possible mechanism of the crosstalk between gut microbes and brain in Parkinson's disease with a focus on immunological mechanisms, specifically the toll like receptor 4.

There is a high need for additional therapies for Parkinson's disease that reduce both motor and non-motor symptoms. A poor gut function leads to a poor brain function and vice versa; therefor targeting the gut-immune-brain axis with nutritional interventions or/and pharmaceutical compounds can be a new approach for the (additional) therapy of Parkinson's disease for the treatment of both motor and non-motor dysfunctions. Fecal transplantation, probiotic and synbiotic therapies target the intestinal microbiome and during the talk (pre)clinical data will be presented. In addition, supplementation with nutritional precursors and cofactors shown to improve synapse function in Alzheimer disease, combined with prebiotic fibres, has therapeutic effects in a mouse model for Parkinson's disease and improved the effect of oral L-DOPA therapy. This and other reports indicate towards important diet-microbiota-pharma interactions in Parkinson's disease.

Figure
Schematic representation of Braak's hypothesis of Parkinson's disease. Microbial products come into contact with olfactory and/or enteric neurons, which trigger the aggregation of α-Synuclein (1 and 2). The aggregated α-Synuclein spreads toward the central nervous system via the olfactory bulb and the vagus nerve (3 and 4). Eventually, the aggregated α-Synuclein arrives at the substantia nigra (5). Genetic factors are likely to contribute to PD, but the exact mechanism remains to be elucidated (6). Rietdijk et al, Frontiers in Neurology 2017



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Prof. Dr. Aletta Kraneveld

Prof. Dr. Aletta Kraneveld studied pharmacy at the University of Amsterdam and Utrecht University. As a junior researcher she worked in the Gastrointestinal Pharmacology Department of Glaxo Group Research in the United Kingdom (1990-1991). She obtained her PhD at the Department of Pharmacology, Faculty of Pharmacy, Utrecht University (1994), after which she continued her research at the Department of Pathology, Harvard Medical School Boston MA, USA (1994). As a postdoc, she continued her research as an immunopharmacologist in Utrecht. In 1998 Aletta was appointed as assistant professor, and in 2002 as associate professor in the Pharmacology division of the Department of Pharmaceutical Sciences, Faculty of Science of Utrecht University.

In 2016, Aletta Kraneveld was appointed professor of Interdisciplinary Translational Pharmacology at the Faculty of Science and the Faculty of Veterinary Medicine of Utrecht University. In addition to science, she is/was an active member of various boards of (inter)national scientific and social organizations (Dutch Society of Pharmacology, FEDERA, EPHAR, IUPHAR, Dutch Federation of Innovative Medicines Research; Nutrition-Leeft; Diversity Committee Utrecht University; Committee on Scientific Integrity Utrecht University). Since 1 March 2020, Aletta Kraneveld has been appointed Vice Dean for Research at the Faculty of Science, Utrecht University, as a result of which her appointment at the Faculty of Veterinary Medicine has ended.

Dr. Kraneveld's current research interests concern the study of the interaction between innate and adaptive immunity, as well as host-microbe interactions in chronic (inflammatory) diseases and treatment with pharmaceutical and nutritional interventions. The Kraneveld group focuses on in-depth research into the role of the gut-immune system-brain axis to enhance knowledge about the interaction of gut microbiota, the immune system and the nervous system in chronic (inflammatory) diseases in the gut, respiratory tract and CNS (neurological and neurodegenerative disorders). With advanced in vivo and in vitro models the Kraneveld group has gained more insight into the importance of the gut microbiota, their ligands/metabolites and associated receptors, the gut mucosal immune system in the tuning of the systemic immune system, with implications for local and external organ functions such as lung and brain. Aletta Kraneveld has set up a research program that became an (inter)national neuro-immune platform where academics, patient organizations and industry meet related to research on the gut-immune-brain axis, as a target for pharmaceutical and medical food concepts.

IBS: IS IT ALL BETWEEN THE EARS?

Francisco Guarner
Teknon Medical Centre, Barcelona, Spain

A large proportion of patients in clinical practice complain of recurrent abdominal pain and discomfort, associated with bloating, abdominal distension, flatulence, and altered bowel habits. In the absence of organic disease, the symptom cluster is classified as IBS. Visceral hypersensitivity is currently the main hypothesis to explain the origin of the symptoms. Increased trait anxiety as well as comorbidity with psychiatric syndromes and other chronic pain syndromes are also common among IBS patients, further indicating the involvement of the brain-gut axis in the generation of cardinal symptoms.

Recent experimental and observational studies support bidirectional interactions between the gut microbiome (microbes and microbial derived products) and the nervous system, both CNS and ENS. We investigated the relationships among diet, abdominal sensations, gas evacuation and colonic microbiota in healthy individuals and in patients complaining of flatulence. In patients, meal-induced symptoms such as bloating, distention and pain, were found to be linked with microbial instability. The diet rich in fermentable vegetables induced abdominal symptoms, and patients' gut microbiotas developed instability in composition, exhibiting variation in abundance of the dominant genera and reduction of microbial diversity. In contrast, healthy subjects showed minor or no symptoms and their gut microbiotas were stable. In patients, but not in healthy individuals, the volume of gas evacuated correlated with abundance of Bilophila wadsworthia in faecal samples. This species is bile-tolerant and generates hydrogen sulphide, which is an irritating gas that may induce symptoms. The study suggested that symptomatic responses may be due to insufficient adaptation of gut microbial metabolic networks for processing plant-food substrates.

Digestive sensations depend on the balance between the gut content (intraluminal stimuli) and tolerance, i.e., the way the intraluminal content is sensed and managed by the gut. Conceivably, a robust gut microbiome improves tolerance of plant-based diets.

Prof. Francisco Guarner

Prof. Francisco Guarner graduated in Medicine at the University of Barcelona in 1973, trained Gastroenterology and Hepatology at Hospital Clinic (Barcelona); obtained PhD degree at University of Navarra (Spain). He was Research Fellow at Royal Free Hospital (London, UK), King's College Hospital (London, UK), and Wellcome Research Laboratories (Beckenham, UK). He is Consultant of Gastroenterology at the Teknon Medical Centre (Barcelona, Spain). Member of the Steering Committee of the International Human Microbiome Consortium (www.human-microbiome.org), member of the Scientific Committee of Gut Microbiota for Health Section of the European Society of Neurogastroenterology and Motility (www.gutmicrobiotaforhealth.com), and past member of the Board of Directors on the International Scientific Association for Probiotics and Prebiotics (isappscience.org). Co-author of 335 publications on original research or reviews (Web of Science), holds an h-index of 65.
https://publons.com/researcher/4053457/francisco-guarner/

HOW MICROBES AFFECT DEPRESSION: UNDERLYING MECHANISMS VIA THE GUT - BRAIN AXIS AND THE MODULATING ROLE OF PROBIOTICS

Kazunori Matsuda
Laboratory Manager, Yakult Central Institute, Tokyo, Japan

Major depressive disorder (MDD) is a common but serious mental disorder characterized by symptoms such as depressed mood, anhedonia, fatigue, anxiety, irritability, insomnia, altered appetite, and suicidal ideation. Although the etiologies underlying this disorder remain unclear, several hypotheses have been proposed to explain the underlying mechanisms of its pathogenesis. The monoamine hypothesis, which holds that depression arises from monoamine deficiency, has dominated research into the pathophysiology and pharmacology of MDD for decades. The monoamine hypothesis is now considered to be part of the pathogenic mechanism of depression or its result, and it has become evident that multiple factors are intricately involved in the pathogenesis of depression, and disorders of the hypothalamus-pituitary-adrenal (HPA) axis involved in stress response, and neurogenesis/neuroplasticity dysfunction involving brain-derived neurotrophic factors (BDNF), have both been proposed as new hypotheses for the cause of depression. In addition to these factors, association between the gut microbiome and mental illness is being discussed. Recent findings suggest that the gut microbiome influences the brain functions and psychological state of its host via the gut–brain axis and gut dysbiosis has been linked to several mental illnesses, including MDD. Short-chain fatty acids such as butyrate produced by the gut microbiome are known to contribute to the up-regulation of BDNF, and gut dysbiosis causes decreased levels of BDNF, which could affect neuronal development and synaptic plasticity. Increased gut permeability causes an influx of gut microbial components such as lipopolysaccharides, and the resultant systemic inflammation may lead to neuroinflammation in the central nervous system.

Several studies have shown that depressive symptoms improved in patients with irritable bowel syndrome when treated with fecal microbiota transplantation (FMT). FMT is considered to restore or reconstruct the gut microbiome, and thus contribute to the amelioration of gastrointestinal and neuropsychiatric symptoms. In addition to the structural modulation of the gut microbiome, a therapeutic approach focusing on the characteristics of specific bacteria is now applied to psychiatric diseases, including MDD. The use of probiotics, as represented by lactobacilli and bifidobacteria, is being identified as a promising way to prevent gut dysbiosis and to maintain or restore physiological homeostasis in the immune system, and its role appears now also to include maintenance of psychological homeostasis via the microbiota–gut–brain axis. Lacticaseibacillus paracasei strain Shirota (LcS; basonym, Lactobacillus casei strain Shirota), for example, suppressed stress-induced increases in salivary cortisol levels in a human academic stress model by modulating the gut–brain axis[1]. An open trial using LcS in patients with MDD or bipolar disorder has shown significant reduction in depressive symptoms after the probiotic treatment, and which was associated with the gut microbiome and more pronounced when Bifidobacterium and the Atopobium cluster of the Actinobacteria phylum were maintained at higher counts[2]. The use of butyrate-producing bacteria is also attracting attention as a promising therapeutic approach for depression, in terms of their ability for the maintenance of neurogenesis and the modulation of inflammation.

This talk describes possible mechanisms underlying the onset of MDD that can be mediated by the gut–brain axis, focusing on an abnormal stress response, decreased neurogenesis, and neural inflammation; and discusses candidate interventions that may modulate the pathophysiology of depression, with a focus on the use of probiotics including lactobacilli, bifidobacteria, and butyrate-producing bacteria.

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Key words: gut microbiome; gut–brain axis; depression; probiotics

Dr. Kazunori Matsuda

Dr. Kazunori Matsuda is a Laboratory Manager at the Food Research Department, Yakult Central Institute in Tokyo, Japan. He started his career at Yakult in 2003, working in the research on the gut microbiota and its roles in human health and disease. He was assigned to Yakult Honsha European Research Center for Microbiology (YHER) in Belgium as Senior Researcher from 2013 until 2018. There he worked on the research to evaluate the effects of probiotics on the regulation of gut function, and conducted clinical trials intended to substantiate health claims on probiotics in the EU countries. He received a Master of Science degree in Agriculture from Kobe University Graduate School of Science and Technology, and obtained his PhD degree in Veterinary Science from The University of Tokyo. His main research interest today is how the gut microbiota and probiotics affect mood, sleep and stress levels of the host through the gut–brain interaction. His research includes clinical trials to test the efficacy and wider applicability of probiotics intervention to promote human mental health, as well as the small-scale experimentations to determine the possible mechanisms of its action.

OVERCOMING THE BRAIN BARRIER: A CHALLENGE FOR BACTERIA?

Prof. Roosmarijn Vandenbroucke
Flanders Institute for Biotechnology, Belgium

Prof. Dr. Roosmarijn Vandenbroucke

Prof. Dr. Roosmarijn Vandenbroucke obtained a Bachelor degree in Biology at the KULAK university in Belgium in 1999, a Master in Biotechnology at the University Ghent in 2001 and a PhD at the same university in 2008, with research work entitled “Non-viral Delivery Strategies to Guide Therapeutic Nucleic Acids through Cellular Barriers”. Dr. Vandenbroucke performed postdoctoral research at the Flemish Institute of biotechnology (VIB), Department of Molecular Biomedical Research, Molecular Mouse Genetics Unit (MMG) in the laboratory of Prof. Dr. Claude Libert, where she became an Assistant Professor in 2014.

Dr. Vandenbroucke is currently associate professor at Ghent University (Department of Biomedical Molecular Biology, Faculty of Sciences, Ghent University, BE) and group leader at VIB (Inflammation Research Center; IRC). Dr. Vandenbroucke is member of many Societies (ESGCT,SoN,BIS, ISEV, ESS, ECCO, GGIG and AcademiaNet) and authored or co-authored more than 180 papers.

Her research focusses on the effects of systemic inflammation (including sepsis/SIRS or other inflammatory stimuli such as (inflamm)aging) and neuroinflammation (such as the age-related diseases Alzheimer’s and Parkinson’s disease) on the blood-CSF barrier. Tight barriers form the major protection for the brain against external insults such as toxins, infectious agents and peripheral blood fluctuations. These brain barriers are a central part of the brain homeostasis mechanism and assure a balanced and well-controlled micro-environment around synapses and axons in the central nervous system (CNS). Although largely understudied, the choroid plexus epithelium, forming the blood-cerebrospinal fluid (CSF) barrier, is an important and unique single layer of epithelial cells situated at the interface between blood and brain. Subtle changes in the choroid plexus epithelial cells, via changes in the CSF composition, have wide-ranging effects on the brain and will subsequently affect disease progression. Therefore, understanding blood-CSF barrier functionality under physiological and pathophysiological conditions might open up new therapeutic strategies to treat inflammatory diseases.

GUT MICROBIAL DIVERSITY: ONE HEALTH AND PROBIOTICS

Olaf F.A. Larsen
Vrije Universiteit Amsterdam, The Netherlands

The integrity of the gut microbiota is intimately related to the onset and progression of disease. In this presentation, new epidemiological data will be presented, showing a profounds increase in both autoimmune and metabolic indications. Together with the emergence of new infectious disease, these data hint towards a progressive deterioration of the status of the gut microbiota. The data will be put into the context of a One Health approach, and the first steps towards a rational intervention to restore key taxa and functionalities within the gut microbiota will be presented.

Dr. Olaf F.A. Larsen
Olaf Larsen studied chemistry at the VU University Amsterdam and obtained a PhD in physics there as well. Following postdoctoral research in New York City and Amsterdam, he continued his career within industry. Olaf worked for ASML, TNO and as a consultant life sciences within various organizations. Since 2012 he is heading the Science department at Yakult Nederland B.V., and member of the Management Team. Since 2016, he is also part time Ast. Professor the VU University focusing on the valorization and computational modelling of microbiota management.

OPPORTUNITIES RELATING TO FERMENTED FOODS

Paul Cotter
Teagasc Food Research Centre; APC Microbiome Ireland & VistaMilk SFI Research Centres, Ireland

This presentation will focus on the opportunities around fermented foods, where the gaps exist, and how the latest science is helping us to fill these gaps
Key take home messages:

- A tremendous variety of fermented foods are produced by all societies globally
- There are still many fermented foods that have yet to undergo in-depth analysis (microbiome or otherwise) to determine their health-promoting and other attributes
- An even small subset of fermented foods have been the focus of pre-clinical/clinical studies
- Despite this, the studies that have taken place show a huge untapped potential
- There are tremendous opportunities to optimise this potential and ensuring quality control, including through combining specific strains with particular attributes

Prof. Paul Cotter
Prof. Paul Cotter is the Head of Food Biosciences at Teagasc and a Principal Investigator with the large Irish Research Centres, APC Microbiome Ireland, Vistamilk and Food for Health Ireland and CTO/co-founder of SeqBiome, a microbiome sequencing and bioinformatics service provider. He is a molecular microbiologist, with a particular focus on the microbiology of foods (especially fermented foods), the food chain and of humans, as well as probiotics and postbiotics. Prof. Cotter is the author of >350 peer-reviewed, was included in the Clarivate list of highly cited researchers for 2018-2021 and is the Field Chief Editor of Frontiers in Microbiology.

DEVELOPMENT OF THE INFANT MICROBIOTA: FROM BIFIDO-DOMINATED TO A DIVERSITY AND RESILIENT ECOSYSTEM

Christophe Lacroix
ETH Zurich, Laboratory of Food Biotechnology, Department of Health Sciences and Technology (HEST), Switzerland

A diverse and complex microbial ecosystem progressively develops after birth, which influences health profoundly in later life. Factors reported to influence the development of the infant gut microbiome (GM) include delivery mode, gestational age, host genetics, feeding regime and perinatal antibiotic usage. The extremely chaotic inter-individual variability reported in most ecological studies on infant GM presents a challenge to establish the link between infant GM and gut health and disease. Hence, it is also important to study the functional capacity of the GM, where different bacteria, possibly belonging to distant taxonomic groups, can perform redundant functions, i.e. metabolize the same substrate. Most studies on infant microbiota targeted the initial colonization period from birth to 6 months of age with focus on taxonomic composition. However, functional aspects of this ecosystem remain little explored. This presentation will attempt to summarize the microbiome taxonomic, diversity and functional development of healthy infant gut microbiome from a high individual to a diverse and resilient ecosystem during the first 2 years of life.

Human milk is the optimum first food for microbiome evolution and provides a high load of oligosaccharides which specifically promote the growth of certain species of bifidobacteria, and of diverse microbes (estimated at log 4 to log 8 viable bacteria/day). Despite this considerable diversity of human milk bacteria, their impact on neonatal gut microbiota establishment, gut maturation, immunity development and consequences on later health status, remain largely unknown.

In the infant's gut, several microbial functional groups work in harmony in a so-called trophic chain to metabolize different sources of carbohydrates reaching the colon and forming end metabolites, mainly acetate and propionate. Most primary colonizers in the infant's gut are lactate-producing bacteria (LPB), including Bifidobacterium, Lactobacillus, and Bacteroides ssp. Lactate is produced in large amounts in the infant's gut and must be re-used by lactate-utilizing bacteria (LUB) to avoid detrimental consequences of lactate accumulation. However, little is known about the LUB community in infants and their impact on gut health. We demonstrated metabolic cross-feeding of lactate and identified keystone species specified for lactate utilization. The interactions of such species and their metabolic outcome could have direct impacts on infant health, either beneficial (production of short chain fatty acids, acetate, propionate and butyrate) or detrimental (accumulation of hydrogen or hydrogen sulfide).

Important dynamic changes of the GM and colonization of functional groups involved in lactate metabolism and butyrate production occur during the period from 6 months to 2 years. Only a few studies have investigated the changes occurring in the GM composition and metabolism during the "critical window" of 6–12 months corresponding to a transition in the infant diet. In a longitudinal infant cohort study, we showed that a switch in the predominant LBP and LUB, from Veillonella producing propionate in the first year to Anaerobutyricum hallii producing butyrate in the second year of life with increased fecal butyrate. Correlation analyses further suggested the metabolic cross-feeding of hydrogen in infants with consequences on bloating.

The healthy infant GM in the first 2 years of life is highly flexible, and hence provide the potential for stirring its development via dietary factors for modulation toward long-lasting health.

Prof. Dr. Ing. Christophe Lacroix

Prof. Dr. Ing. Christophe Lacroix, Head of the Laboratory of Food Biotechnology, Institute of Food, Nutrition and Health, Department of Health Sciences and Technology (D-HEST), ETH Zurich, Zürich, Switzerland
Christophe Lacroix studied Food Engineering at AgroParisTech (1980).and obtained a PhD in Food Science (1984) and was Professor of Dairy Biotechnology at the Université Laval, Quebec (1984-2002). He was a founder (1986) and lead (from 1995 to 2002) the Dairy Research Centre (STELA) in North America and the Canadian Network of Excellence on Lactic Acid Bacteria (1997-2002). Prof. Lacroix won a number of honors and awards, including the first Canadian Millennium Chair in Food Sciences and Nutrition (2001). He was Visiting Professor at INRAE France (1992-93), invited scientist at the Nestlé Research Center Lausanne (1999-2000), and participated in many international evaluation committees for research programs and institutions.

His research work in the field of microbial biotechnology, including innovative fermentation and downstream processing technologies, development of functional microbes for use in food and biotherapeutic products, gut microbiota fermentation modeling and functional studies, and mechanistic impact of food components and antimicrobials on the composition and function of human and animal gut microbiota. He has published over 330 peer-reviewed articles, 15 patents, and supervised 65 doctoral students. His work has been supported by numerous national and international grants, as well as by a large number of industries worldwide. He is founder and member of the Board of Director and of the Scientific Advisory Board of the ETH-Spinoff company, PharmaBiome AG (2017), specializing in the isolation, functional characterization, design and production technologies of gut microbe-based products for human therapy.

SAFETY OF MICROORGANISMS USED AS PROBIOTICS: WHICH STRATEGIES FOR RISK ASSESSMENT?

Pier-Sandro Cocconcelli
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The process for determining the microbial food safety is generally based on the four canonical steps of the risk assessment (RA): i) hazard identification, ii) hazard characterisation, iii) exposure assessment and iv) risk characterisation, an approach specifically designed for the appraisal of foodborne pathogens, such as Salmonella enterica, Listeria monocytogenes, Clostridium botulinum, STEC or norovirus. In these cases, hazard identification derives mainly from epidemiological data of foodborne infections or intoxications, the hazard characterisation includes the study of the strain causing the outbreak. This step, in the last years, take advantage from the whole genome sequence (WGS) analyses, that provide key information on the nature of bacterial strains responsible for foodborne infections and intoxications. The exposure to these microbes is expected to be sporadic and often related to the ingestion of a limited number of cells.

Typically, these analyses are carried out retrospectively, on strains isolated from implicated foods or patients.
When the same approach is applied to microorganisms intentionally introduced into the food chain, such as animal and human probiotics, limitations arise. Thus, in these cases the assessment should ideally be performed ex-ante, prior to marketing, and it focuses on a limited number of strains, mostly belonging to microbial groups, such as lactic acid bacteria, bifidobacteria and yeasts, known to be non-pathogenic. Furthermore, the RA is carried out on the basis of proprietary data produced by the owner of the probiotic strain and exposure is expected to be high and continuous (e.g. daily ingestion of millions of cells). Consequently, targeted procedures should be applied for the evidence-based RA of microbial cultures used as probiotics.

In recent years, the European Food Safety Authority (EFSA) has developed strategies for the evaluation of microbial products seeking for authorization under EU regulations, e.g. animal probiotics and novel foods. This approach, which has proven to be effective, is now applied outside EFSA and considered internationally as a reference methodology for the safety of microbial cultures.
The pillars of EFSA's RA on microorganisms intentionally introduced into food chains should be summarized as:

- the Qualified Presumption of Safety, that defines a list of taxonomical units (generally species) that are considered safe for any application/use that fall under the remit of risk assessment made by EFSA.
- the absence of acquired resistances to critically important and highly important antimicrobials, mostly limited to bacterial strains
- the WGS analysis, which provides information on taxonomical identification, presence of virulence factors and on of antimicrobial resistance genes
- the safety assessment of the genetically modified microorganisms

The basis of strategies for RA of microbial cultures used as probiotics will be presented, focusing on the advantages and possible limitations. In particular, examples of the WGS based RA and on acquired antimicrobial resistance will be discussed.

Prof. Pier Sandro Cocconcelli

Pier Sandro Cocconcelli is Professor of Food Microbiology and Emerging Food Risks at the Università Cattolica del Sacro Cuore and vice-rector for internationalization of the same university. He is director of TROFIC (the Transdisciplinary Research on Food Issues Center) of the Università Cattolica, a center focusing on transdisciplinary research on food merging competences from different disciplines: Food Science and Technology, Agriculture, Food Risk Analysis, Nutrition, Consumer Perception, Food Law, Communication and Food Economics, and President of CHEI, Centre for Higher Education Internationalization of the Università Cattolica He is the Secretary general of the Strategic Alliance of Catholic Universities, a global network of research universities and President of CHEI, Centre for Higher Education Internationalization of the Università Cattolica. Since 2003, he is scientific expert of the European Authority of Food Safety (EFSA) as Panel and Working Group member focusing on the microbiological risk assessment and on the assessment of genetically modified microorganisms. Has chaired the Standing Working Group on Microorganisms of FEEDAP the Standing Working Group of Genetically Modified Microorganisms and currently chairs the WG on Synthetic Biology Microorganisms of the EFSA Scientific Committee. He is member of the CEP Panel (Food Contact Materials, Enzymes and Processing Aids). He is also member of the BIOHAZ Panel Working Group on Qualified Presumption of Safety of Microorganisms. His research activities focus on food, agricultural and environmental microbiology, food safety, bacterial genomics, risk analysis of food pathogenic bacteria, bacterial bioremediation in the agri-food system. He is the author of more than 500 publications that relate to food and environmental microbiology and food risk assessment and author of book chapters on microbiology.

LIVING FOODS: A SAFE SALVATION FOR HEALTH

Lorenzo Morelli
Head of Department, DISTAS – Department for Sustainable Food Process Faculty of Agriculture, food and environmental sciences. Universita Cattolica del Sacro Cuore, Italy.

Key messages of this presentation will be:
1) microorganisms to preserve nutrients, leading to fermented foods and 2) microorganisms interacting with our body.
Historians have traced signs of fermentation in food and beverage preparation dating as far back as 7000 BC.
The term fermentation comes from the Latin verb fervere, which means "to boil; and we may compare the effect of inoculating microorganisms into raw material to preserve essential nutrients (i.e. proteins) for human consumption but also to enjoy life! (Beer, wine…).

Back slopping was the first "inoculation technique" and it still used in a wide range of food fermentation, such as the Italian most famous Parmesan cheese. The weak point of back slopping is the undefined composition of the microbiota involved, not only for the final quality of the products but also for the safety.

Nowadays is therefore relevant, to have "a safe salvation of nutrients" but also for the food safety itself to have a detailed knowledge of the presence of microorganisms and their safety profile. Some approaches will be showed, such as QPS and GRAS but also the recent "Inventory of microbial food cultures with safety demonstration in fermented food products".
An additional item in which living foods are a safe salvation for health is "biopreservation"; a full range of research approaches is underway to better exploit microorganism to preserve and protect the food, also considering the different way in which food cultures and this application could help tackle food waste as an additional control measure to ensure the safety of the food.

The latter message of this presentation will deal with the use of microorganisms to interact with a range of ecological niches of our body to promote wellbeing. The role played by bacteria into our gut stems from the pioneering works of Elie Metchnikoff and has nowadays a solid science supporting several applications, either as living, active ingredients of food or as drugs or biotherapeutics. A sometimes underestimated role is that one played by the food matrix; the same strains, administered via different food matrices has different behaviour, mainly as rate of survival during the intestinal transit.

Moreover, food fermented with bacteria able to survive and persist into the gut after ingestion, can be considered as natural symbiotic products, where bacteria and fermentation metabolites have a synergistic effect. Some relevant items of research are investigating the role of bacteria outside the gut, mainly the uro-genital tract and ther skin.

Some positive effects are also exerted by bacteria far away the native ecological habitat. Gut-brain axis has now a relevant number of studies, leading to the creation of a new category such a the "psycobiotics" but also the more recently investigated "gut-lung axis".

To conclude it is my opinion that the long history of use of "living foods" and "living ingredients" has a long and bright future ahead of it but we really need solid science to support this future.

Prof. Dr. Lorenzo Morelli

Prof. Dr. Lorenzo Morelli is Dean Faculty of Agriculture, Food and Environmental Sciences at the Università Cattolica del Sacro Cuore, Director Department DiSTAS – Department for Sustainable food process, teaching several courses in food microbiology. Research activities have been focused on the biology and genetics of food related bacteria, with a focus on lactic acid bacteria and bifidobacteria. Since 1982, when he published the first paper on the presence of drug resistance plasmids in Lactobacillus acidophilus and Lactobacillus reuteri, he has followed the evolution of the presence of antibiotic resistance in non-pathogenic bacteria.

Prof. Morelli was the co-ordinator of the first EU (1991) funded project devoted to probiotics (FLAIR project AGRF 0053 “Selection and characterisation of human probiotic strain “) and since that time he has a track record of research activity in the field of molecular biology applied lactic acid bacteria. Many EU research projects have followed (Deprohealth, Infabio, Ace-art,…). Molecular taxonomy of lactic acid bacteria is another field of interest, with a focus on molecular identification of bacteria from the microbiota of newborn infants.

In October 2001 Prof. Morelli was appointed by FAO/WHO as one out the international experts to prepare the report of the meeting held in Cordoba (Argentina) on the assessment of “Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria”, leading further in 2002 in an FAO/WHO international consultation aimed at establishing the “Guidelines for the Evaluation of Probiotics in Food” (London, Ontario, Canada, April 30 and May 1, 2002).

LIVING DRUGS: A SOLUTION WITH MANY BENEFITS

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Studied human medicine at the Johannes Gutenberg University Mainz and the Université Louis Pasteur Strasbourg. 1989 license to practice medicine and doctorate, scientific assistant at the Institute for Clinical Immunology, University Hospital Bern/Switzerland. 1992 Resident in the Department of Gastroenterology & Hepatology, Hanover Medical School, 1997 Specialist qualification in internal medicine and additional title “Allergology”, 1998 Habilitation in internal medicine, sub-specialty title “Gastroenterology”, 2001 Specialist qualification “Nutritional Medicine”. 2002-2003 Visiting Professor at Columbia University, New York. 2004 Appointed Full Professor and Chair of Nutritional Medicine and Prevention at the University of Hohenheim in Stuttgart. 2006 Chairman of the German Society for Nutritional Medicine. 2009 Medical Director of the Center for Nutritional Medicine at the University Hospital of Tübingen and the University of Hohenheim. 2010 Editor of the journal Aktuelle Ernährungsmedizin. 2012 President of the German Society for Nutritional Medicine.

Clinical-scientific focus:
- Obesity and obesity-associated diseases.
- Disease-associated malnutrition and artificial nutrition
- Gastrointestinal barrier, mucosal immunology & neurogastroenterology
- Probiotics and functional food
- Food allergies and intolerances, mast cell research
- Health prevention through nutrition, gender research

THE IMPORTANCE OF THE RESPONDER / NON-RESPONDER ISSUE FOR CLINICAL TRIALS WITH PROBIOTICS. IS THE TRADITIONAL RCT DESIGN ADEQUATE?

Robert-Jan Brummer
Örebro University, Sweden

Terminology like “personalised nutrition” or “precision nutrition” are widely used in relation to individual health effects of diet. However, how this evidence of individual health effects is achieved often lacks precision. In practice, epidemiologic studies build the major basis for dietary recommendations, although we know that evidence from these studies often is hard to reproduce in prospective randomised trials. Another critical issue is that dietary recommendations mainly are directed to groups of subjects rather than individuals. Hence, dietary randomised clinical trials should be used to create bespoke recommendations. However, we are well aware of many, often underpowered, negative outcomes although the initial hypothesis was very promising.

This lecture discusses the various reasons for the negative outcomes of many dietary clinical trials in general and probiotic studies particularly. It also elucidates the clear differences between a food or pharmacologic intervention and clarifies the limitations of randomised clinical trials from a food/food supplement perspective.

This leads to the issue of inter- versus intra-individual variation of biomarkers as well as the choice of so called “surrogate” biomarkers and consequently the importance of responder versus non-responder. The novel concept of “responsive nutrition” is highlighted and discussed. Its focus is on the characterisation of a responder subject versus a non-responder subject rather than a group versus an individual. Also the importance of reliable so called “surrogate” biomarkers will be discussed. It becomes clear that the traditional randomised clinical trial design infers clear weaknesses if applied to food, pre- and probiotics. On basis of this analysis, suggestions for improvement are presented.

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Prof. Robert-JM Brummer

Prof. Robert-JM Brummer studied medicine at Nijmegen University, the Netherlands and performed his PhD studies in Göteborg, Sweden (PhD 1992) and continued clinical training in internal medicine and gastroenterology at University Hospital Maastricht, the Netherlands. He became professor at Maastricht University 2002 and was acting director of the nutrition research institute (NUTRIM) of the University. Subsequently, he became research director at the "Wageningen Centre for Food Science", later "TI Food and Nutrition", the Netherlands.

From 2008 he joined Örebro University, Sweden as professor of Gastroenterology and Clinical Nutrition and senior consultant at the University Hospital. Brummer was Dean of the Faculty of Medicine and Health during 6 years and currently is Pro-Vice-Chancellor of the University. In that role he also is director of the Örebro University Food & Health Programme. He leads both the interdisciplinary "Nutrition-Gut-Brain Interactions Research Centre" at the University as well as the recently governmentally funded national research excellence centre "Plant-based Proteins for Health and Wellbeing – PAN Sweden". Furthermore, he is engaged in national boards and strategies regarding food and nutrition research and innovation and acts as reviewer for several international research councils and represents Sweden in the European Universities Association expert group on innovation.

His main field of interest in research is the nutrition/microbe-gut-brain interactions with special reference to human application and still performs all research endoscopic investigations himself.

MICROBIOTA COMPOSITION FROM 1 TILL 100

Gaspar Pérez Martínez
Instituto de Agroquímica y Tecnología de Alimentos (CSIC), Valencia, Spain

Microbial colonization starts at birth, during lactation and in the first stages of life, when our organism is exposed to large armies of bacteria coming from milk, family members and surrounding objects, and which will have a direct effect on the training and development of the immune system. In the following years, microbial populations in the gut become more or less stable until adulthood, influenced by some genetic factors and with remarkable changes in the microbiome associated to the gut function. Then, the microbiome may suffer detrimental changes associated to ageing, frailty and immune senescence. This would be an ideal, but simplified, conducting thread of a life long coexistence with our gut microbiome, but the abundance of conditioning factors suggest that exceptions may in fact be the rule and during life. Starting from early life, interaction with the microbiome may occur already during pregnancy, a fact that seriously under debate. The environment is a powerful driver of the microbiome composition, remarkably the urban environment reduces bacterial microbial gut diversity and the contact with animals has a powerful influence on the risk of allergic rhinitis in children. Diet is also a powerful driver of microbial composition and diversity. It is known that vegetarian or Mediterranean diets promote a healthy status associated to specific bacterial populations; interestingly those populations that can be stimulated just in a few days of intervention. Antibiotic treatments sensibly modify the microbiota composition and, after sustained or massive antibiotics treatments, microbiome resilience may be lost, that is, changes in bacterial profiles may persist after the treatment, a situation that has been bound to increasing the risk of allergies, obesity and non-communicable diseases. Human life expectancy has been extended, and the possibility to live till 80-90 years is no longer out of reach. But likely changes take place during ageing that influence and are influenced by the gut microbiota, in fact all studies on older persons show that age, above all factors, is the measureable variable that has a stronger correlation with changes in the microbiota. These findings have two exceptions: unusually healthy elderly have similar microbiota to normal healthy adults; and centennials, in which a particularly balanced microbiota is maintained.

Further, abundant research demonstrate that the organism is not a set of independent compartments and that the metabolic activity of the microbiota participates in the brain-gut axis communication and regulation of endocrine secretions. Under pathological conditions, gut permeability favours the presence of pathogens and gut bacteria in circulating blood, as well as bacterial extracellular vesicles. But also under normal, healthy conditions, selective trans-organic migration of specific mucosal associated microorganisms takes place to colonize the mammary gland and other internal organs. As a matter of fact, endocytosis and transcytosis of beneficial and probiotic bacteria through the gut epithelium has long ago been demonstrated, which could be the initiation of this process. Commensal endocytosis also results in the intracellular survival of harmless bacteria for several days, for which this process could be related not just to trans-organic migration, but also to commensal tolerance or gut microbiota resilience. Extracellular vesicles have been mentioned and they may be playing some interesting roles in the organism. In the gut ecosystem there are abundant bacterial EV that may have biological effects, as proven in the case of different probiotics (E.coli Nissle 1927, L. reuterii, Bifidobacterium lactis and A. muciniphila), and given their small size, they could be easily diffused in the bloodstream and they could trespass important barriers, like the mother's the placental barrier. These facts highlight that we are very complex organisms and the limits of the influence of the microbiome on our health and body functions have not yet been discovered.

Prof. Gaspar Perez

Prof. Gaspar Perez studies Biology at the Universidad de Valencia, Valencia, Spain (1974-1979), after which he made a PhD in microbiology at the University of Nottingham, Nottingham, UK (1981-1985). During subsequent postdocs at the University of Groningen, Groningen, the Netherlands and the University of Tübingen, Tübingen, Germany, Prof. Perez got more diverse research experience in the field of microbiology and extended his network throughout Europe, allowing him to obtain and execute 5 successful European projects (1992-2004) and 4 projects from the CICYT (Spanish Government). Since 1990, Prof. Perez had focused his research on the fermentative metabolism of Lactic Acid Bacteria in food fermentations and their probiotic activity. New expertise in Molecular methodologies and Genomics of Food Microorganisms allowed the smooth transition to the field of gut microbiota, including the second generation of massive sequencing analysis, still keeping an eye on the biotechnology aspects and trying to identify mechanisms that underlay host/bacteria interactions.

At the laboratory of lactic acid bacteria in the IATA-CSIC has consolidated multiple collaborations with many relevant research groups in the field in Europe, focussing on three main project lines: (i) Bacteria/Host molecular interactions; (ii) Microbiome, Diet and Health; and we do not forget our history (iii) LAB in Food Fermentations.
Prof. Perez also participated in different projects with industries, obtained functions in Scientific Advisory Committees of national and international institutions, and in the creation of Spinoff Company (AFT, S.L.) for the production of probiotic fermented vegetable products (EU Patent: Nº 05743929.1).

His personal interests is on understanding the molecular dialogue of beneficial gut bacteria with the host, in particular lactic acid bacteria, their anti-inflammatory and anti-apoptotic activity, focusing on a variety of wall bound bacterial proteinases (PrtP) or cell wall lysines (P40, P75) and extracellular vesicles.

Prof. Perez is currently Head of laboratory “Instituto de Agroquimica y Tecnologia de Alimentos, at the “Consejo Superior de Investigaciones Científicas (CSIC)”, Valencia, Spain.

GUT MICROBIOTA CHANGES IN THE EXTREME DECADES OF HUMAN LIFE: A FOCUS ON CENTENARIANS

Patrizia Brigidi
Department of Medical and Surgical Sciences, Alma Mater Studiorum-Università di Bologna, Italy

Longevity has been described as the result of a complex combination of variables, deriving from genetics, lifestyle, and environment. In this context, the intestinal microbiome has been proposed as a possible mediator of healthy aging that preserves host-environment homeostasis by counteracting inflammaging, intestinal permeability, and deterioration of cognitive and bone health. Indeed, correlations have been found between age-related gut microbiota dysbioses and levels of proinflammatory cytokines, hospitalization, poor diet, and frailty in the elderly[1].

In this scenario, to unravel the functional and taxonomic links between gut microbiome and extreme aging, we explored the longest available human microbiota trajectory along aging, characterizing the fecal microbiome of individuals of different ages [young adults (22-48 y), elderly (65-75 y), centenarians (99-104 y) and semi-supercentenarians (105-109 y)], by a shotgun metagenomics approach to extend the profiling down to species level and provide an accurate depiction of the functional changes occurring along with age.

We showed that there is a core microbiota of highly occurring, symbiotic bacterial groups, which remains approximately constant during aging but varies in the cumulative relative abundance of its members. Centenarians and semi-supercentenarians were featured by a distinctive rearrangement in their microbiome configuration, with increasing abundance of subdominant species as well as a rearrangement in health-associated bacteria. Furthermore, peculiarities emerged, especially in semi-supercentenarians, describing changes that, even accommodating opportunistic and allochthonous bacteria, might possibly support health maintenance during aging[2].

At a functional scale, gene rearrangements in metabolic pathways related to carbohydrate, amino acid and lipid metabolism as well as xenobiotics degradation were evidenced in centenarians and even more in semi-supercentenarians, probably representing the result of a life-long adaptive response to progressive changes in diet and lifestyle.

With age, we observed a reduced contribution of pathways for starch and sucrose, pentose phosphate, and amino sugar and nucleotide sugar metabolism and a concomitant increase in genes for the metabolism of tryptophan, tyrosine, glycine, serine, and threonine, an indicator of enhanced proteolytic metabolism. Interestingly, in long-lived people we found a progressive increase in toluene, ethyl- benzene, caprolactam, and chlorocyclohexane and chlorobenzene degradation pathways which might be the result mainly of a top-down selection process related to the lifestyle habits of these exceptionally old individuals[3]. In conclusion, our studies help to shed light on whether the peculiar profiles of gut microbiome of extremely long-lived hosts are capable of supporting a new homeostasis.

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PROBIOTICS AND THE AGEING IMMUNE SYSTEM

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There is a great deal of both public and commercial interest in the potential of foods or supplements to modify immune function, with this interest significantly increasing in response to the covid pandemic. Immune function varies across the lifecourse, with a well understood decline in immune function with age, resulting in impaired vaccination responses and an increased risk of infections and of severe complications and mortality arising from common communicable diseases such as influenza. This impaired immunity with ageing is known as immunosenescence, and affects both innate and acquired arms of the immune system. The gut microbiome is modified by diet and shows changes with ageing, with both direct and indirect interactions with the immune system. Thus, there is interest in whether dietary probiotics might benefit immune function in older adults, acting to prevent or slow the changes associated with immunosenescence.

There is available evidence that probiotics can improve in vivo and ex vivo measures of immune function in older adults. Research to date has included studies of both heat-killed probiotic organisms and live probiotic preparations, typically strains of bifidobacterial or lactobacilli, with typical intervention periods of 3-6 weeks. Reported outcomes of probiotic interventions include reduction in participant infection rates (Mane et al., 2011), duration of common infectious diseases (Guillemard et al., 2010) and reported winter pathologies (Turchet et al., 2003), and reported increases in vaccine-specific antibody responses following influenza vaccination (Akatsu et al., 2013a, Akatsu et al., 2013b, Bosch et al., 2012, Boge et al., 2009), and NK cell activity (Dong et al., 2013, Takeda and Okumura, 2007, Gill et al., 2001a, Gill et al., 2001b). However, few of the studies identified used immune outcome measures designed to directly assess markers of immunosenescence such as TRECs or the proportions of memory and naïve T cell phenotypes. Data indicates that 'older adults' are not a homogenous group, with subgroup specific effects observed among the 'oldest old' or those with a lower baseline immune function. There is an indication that these subgroups of 'oldest old' or immunocompromised adults respond more strongly to probiotic treatment (Gill et al., 2001a, Parra et al., 2004, Gill et al., 2001b, Maruyama et al., 2016).

My research examines the interaction between the gut, immune system and symptoms of health and disease. It is a significant challenge to design rigorous human nutrition trials - how can we account for background intakes, varying body composition, immune age or indeed identify a suitable 'placebo' or control group? It will be a challenge for future nutrition research to ensure that both gut microbiome assessment and immunosenescence markers are included when conducting studies of older adults. Inclusion of immunosenescence markers is particularly important given that variations in the degree of immunosenescence among older adults at baseline is a significant potential confounder (Przemska-Kosicka et al., 2016). Interdisciplinary research will be key to fully engaging with the potential impacts of probiotics upon the immune system.

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Poster Presentations

EARLY-LIFE GUT MICROBIOTA AND NEURODEVELOPMENT IN PRETERM INFANTS

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Background
Proper assembly of the gut microbiota is important for the child's long-term health, but the relationship with neurocognitive development has not yet been fully explored.

Methods
Here we conducted a pilot observational study in very low birth weight preterm infants, searching for associations between developmental dynamics of the gut microbiota in the first month of life and neurodevelopment, assessed at 24 months of corrected age.

Results
Compared to preterm infants with normal neurological development, those with adverse neurological outcomes were featured by distinct gut microbiota trajectories and peculiar compositional rearrangements. In particular, the absence of *Bifidobacterium* at 30 days of life was associated with neurodevelopmental impairment.

Discussion and Conclusion
Early Bifidobacterium deficiency in the gut microbiota of preterm infants could act as a biomarker of adverse neurological outcomes. Once confirmed in larger cohorts, our findings could pave the way for the design of early microbiome-based intervention strategies to modulate altered profiles and promote optimal neurodevelopment, for long-term health of these fragile infants.

Funding and/or conflict of interest
None.

GUT MICROBIOTA PROFILE OF STUNTED AND NORMAL NUTRITIONAL STATUS CHILDREN IN JAVA AND EAST NUSA TENGGARA

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Background

Stunting has become a major health problem in the world. Gut microbiota has close links to food digestion, food absorption and intestinal function. Dysbiosis of gut microbiota in children may predispose to stunting.

Methods

The difference in gut microbiota composition of stunted Indonesian children and those of normal nutritional status 3-5 years in Java and East Nusa Tenggara were investigated. Seventy-eight stunted and 53 children with normal nutritional status in two regions in Java (Pandeglang and Sumedang) and 100 stunted and 100 children with normal nutritional status in two regions in East Nusa Tenggara (Kupang city and North Kodi district) were included. The gut microbiota composition was determined by sequencing amplicons of the V3-V4 region of the 16S rRNA gene and correlated to nutritional status and anthropometric parameters.

Results

On Java, at phylum level the relative abundance of Bacteroidetes in stunted children (44.4%) was significantly lower than in normal children (51.3%; p-value $2.55*10^{-4}$), while Firmicutes was significantly higher (45.7% vs. 39.8%; p-value $5.89*10^{-4}$). At the genus level, overall *Prevotella 9* was the most abundant genus (average of 27%), and significantly lower in stunted children than in normal children (23.5% vs. 30.5%, respectively; p-value 0.059). Thirteen other genera were significantly different between stunted and normal children (p-value < 0.1). *Prevotella 9* positively correlated with height, in line with its higher relative abundance in normal children.

In East Nusa Tenggara, the phyla Bacteroidetes (p= 0.014) and Cyanobacteria (p= 0.049) were significantly higher in stunted children. Three taxa at genus levels were consistently significantly higher in stunted children at both sampling sites, namely *Lachnoclostridium*, *Faecalibacterium* and *Veillonella* (p < 7 * 10-4). These and 9 other taxa positively correlated to the z-score length-for-age (zlen), while 11 taxa negatively correlated with zlen.

Discussion and Conclusion

The relationship between gut microbiota and stunting is complex and influenced by many confounding factors. The profiles of stunted children in East Nusa Tenggara and those in Java are non-congruent, due to differences in cultural habits, and infrastructure facilities such as clean water and sanitation, which may contribute to the differences observed.

Keywords

stunting, microbiota, gut health

Funding

The study was funded by a) National Research Priority Scheme, contract Number: 022/E4.1/AK.04.PRN/2021, b) the Centre for Healthy Eating & Food Innovation (HEFI) of Maastricht University – campus Venlo, which has been made possible with the support of the Dutch Province of Limburg.

Conflict of interest

None.

THE ESTABLISHMENT OF THE GUT MICROBIOTA IN 1-YEAR-AGED INFANTS: FROM BIRTH TO FAMILY FOOD

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Background/Introduction

With the aim of characterizing the gastrointestinal (GI) microbiota and contextually determine how different prenatal, perinatal, and postnatal factors affected its composition in early childhood, infants were enrolled in a longitudinal prospective study named "A.MA.MI." (Alimentazione MAmma e bambino nei primi MIIle giorni; NCT04122612, October 2019)[a].

Methods

Forty-five fecal samples were collected at 12 months of infants' age, identified as the 3rd follow-up (T3). The evaluated variables were pre-gestational weight and weight gain during pregnancy, delivery mode, feeding, timing of weaning, and presence/absence of older siblings. Fecal alpha and beta-diversities were analyzed. Noteworthy, to determine the impact of the influencing factors, multivariate analyses were conducted.

Results

At T3, all prenatal and perinatal variables did not result to be significant whereas, among the postnatal variables, type of milk-feeding and weaning showed the greatest contribution in shaping the microbiota. Although aged 1 year, infants exclusively breastfed until 6 months were mainly colonized by *Lactobacillaceae* and *Enterobacteriaceae*. Differently, *Bacteroidaceae* characterized the microbiota of infants that were never breastfed in an exclusive way. Moreover, although an early introduction of solid foods determined higher values of Faith's PD, high abundances of *Ruminococcaceae* and *Faecalibacterium* mainly associated with infants weaned after the 4th month of age.

Discussion and conclusion

The microbial colonization during the first year of life is likely affected by a simultaneous effect of multiple variables playing a significant role at different times. Therefore, these data contribute to add evidence concerning the complex multifactorial interaction between GI microbiota and various stimuli affecting infants during the early stages of life.
[Results of the present abstract are published on Vacca et al. Eur J Nutr. 2022;61(5):2517-2530].

Keywords

Infant gut microbiota, Feeding, Weaning, Solid food introduction, *Lactobacillaceae, Faecalibacterium*

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Funding and/or conflict of interest

None.

Reference:

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IMPACT OF INFANT FORMULA SUPPLEMENTED WITH BIFIDOBACTERIA AND GALACTOOLIGOSACCHARIDES ON DIURNAL RHYTHMICITY OF THE MICROBIOME IN THE FIRST YEAR OF LIFE

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Introduction

Gut bacterial composition between breastfed and formula-fed infants was previously observed to differ vastly. The first few months of life of a child pose a unique window of opportunity to affect the colonization of the naïve fecal ecosystem. In adults, certain gut microbes were shown to exhibit time-of-day dependent oscillations in terms of relative abundance.

Methods

The double-blind, placebo-controlled intervention study "Infantibio-II" accompanied 210 infants in the greater Munich area from birth until one year of age. Infants (N = 147) were randomized to receive one of four differentially supplemented cows-milk based infant formulas containing either probiotics (*B. breve* and *B. longum infantis*), prebiotics (galactgooligosaccharides), both or no supplements (placebo). A control group of participants (N = 63) were exclusively breastfed. Infant fecal samples were collected at five time points and metadata including time of defecation recorded. Samples were analyzed via 16S rRNA sequencing targeting the V3V4 region, complemented by shallow metagenomics and metabolite analysis of a subset of infant samples at month three and seven.

Results

Galactooliogsaccharide- and *Bifidobacteria*-supplementation effectively increased the abundance of *Bifidobacteria* compared to placebo formula. We demonstrate that abundance of fecal metabolites fluctuates in 24-h oscillations. In the different feeding groups, distinct zOTUs were identified to show diurnal rhythmicity as well as overall richness and the genus *Bifidobacterium*. Synbiotic formula was associated with the highest number of rhythmic pathways at month seven.

Conclusion

Supplementing pro- or prebiotics beats placebo formula at the potential for creating a fecal microbial environment resembling breastfed infants. Despite infants lacking a clear day and night rhythm with regard to feeding and defecation habits, their gut microbiota already displays rhythmic fluctuations in composition.

Funding

Töpfer GmbH is the manufacturer of the infant formula and provided financial support but had no influence on design, execution or data analysis of the study.

LIMIT: LIFESTYLE AND MICROBIOME INTERACTION EARLY ADIPOSITY REBOUND IN CHILDREN, A STUDY PROTOCOL

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Background/Introduction

Childhood obesity is a strong predictor of adult obesity with health and economic consequences for individuals and society. Adiposity rebound (AR) is a rise in the Body Mass Index occurring between 3 and 7 years. Early adiposity rebound (EAR) occurs at a median age of 2 years and predisposes to a later onset of obesity. Since obesity has been associated with intestinal dysbiosis, we hypothesize that EAR could be related to early microbiome changes due to maternal/lifestyle changes and environmental exposures, which can increase the unhealthy consequences of childhood obesity. LIMIT is a prospective cohort study that aims at identifying the longitudinal interplay between infant gut microbiome, infant/maternal lifestyle, and environmental variables, in children with EAR vs. AR.

Methods

The study evaluated 272 mother-infant pairs, enrolled at an Italian neonatal unit, at different time points (T0, at delivery; T1, 1 month; T2, 6 months; T3, 12 months; T4, 24 months; T5, 36 months after birth). The variables that were collected include maternal/infant anthropometric measurements, lifestyle habits, maternal environmental endocrine disruptor exposure, as well as infant AR.

Discussion and conclusion

The LIMIT results will provide the basis for early identification of those maternal and infant modifiable factors on which to act for an effective and personalized prevention of childhood obesity.

[The study protocol is published by De Giuseppe et al. Metabolites 2022, 12(9), 809; https://doi.org/10.3390/metabo12090809]

Keywords

childhood obesity; early adiposity rebound; microbiome; lifestyle; nutrition

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Funding

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Conflict of interest

None.

GUT MICROBIOTA IN MONOZYGOTIC TWINS DISCORDANT FOR PARKINSON'S DISEASE

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Background

Constipation seems to be an important issue in Parkinson's disease and it has been clearly related to a state of dysbiosis. Differences in gut microbiota between Parkinson's disease patients and healthy controls seem to depend on multiple-frequently unmeasured-confounders. Monozygotic twins offer a unique model for controlling several factors responsible for interpersonal variations in gut microbiota.

Methods

Fecal samples from 20 monozygotic twin pairs (n = 40) discordant for Parkinson's disease were studied (metagenomic shotgun analysis).

Results

Paired data analysis detected minimal differences in bacterial taxa abundance at species level (*Bacteroides pectinophilus* [p = 0.037], *Bifidobacterium pseudocatenulatum* [p = 0.050], and *Bifidobacterium catenulatum* [p = 0.025]) and in predicted metabolic pathways (primary bile acid biosynthesis [p = 0.037]).

Conclusions

Additional studies are needed to understand the role of gut microbiota in the pathogenesis of Parkinson's disease. However, there is evidence that a regular intake of probiotics can significantly improve stool consistency and bowel habits in Parkinson's disease patients. Fermented milk containing probiotics may represent a possible easily accessible help to improve constipation and dysbiosis in Parkinson's disease patients.

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THE MICROBIOTA–GUT–BRAIN AXIS: PATHWAYS TO BETTER BRAIN HEALTH. PERSPECTIVES ON WHAT WE KNOW, WHAT WE NEED TO INVESTIGATE AND HOW TO PUT KNOWLEDGE INTO PRACTICE

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The gut and brain link via various metabolic and signalling pathways, each with the potential to influence mental, brain and cognitive health. Over the past decade, the involvement of the gut microbiota in gut–brain communication has become the focus of increased scientific interest, establishing the microbiota–gut–brain axis as a field of research. There is a growing number of association studies exploring the gut microbiota's possible role in memory, learning, anxiety, stress, neurodevelopmental and neurodegenerative disorders. Consequently, attention is now turning to how the microbiota can become the target of nutritional and therapeutic strategies for improved brain health and well-being. However, while such strategies that target the gut microbiota to influence brain health and function are currently under development with varying levels of success, still very little is yet known about the triggers and mechanisms underlying the gut microbiota's apparent influence on cognitive or brain function and most evidence comes from pre-clinical studies rather than well controlled clinical trials/investigations. Filling the knowledge gaps requires establishing a standardised methodology for human studies, including strong guidance for specific focus areas of the microbiota–gut–brain axis, the need for more extensive biological sample analyses, and identification of relevant biomarkers. Other urgent requirements are new advanced models for in vitro and in vivo studies of relevant mechanisms, and a greater focus on omics technologies with supporting bioinformatics resources (training, tools) to efficiently translate study findings, as well as the identification of relevant targets in study populations. The key to building a validated evidence base relies on increasing knowledge sharing and on multi-disciplinary collaborations, along with continued public–private funding. This will allow the microbiota–gut–brain axis research to move to the next phase where we can identify realistic opportunities to modulate the microbiota for better brain health.

POTENTIAL OF LACTIC ACID BACTERIA FOR NEUROLOGICAL HEALTH BENEFITS: GAMMA-AMINOBUTYRIC ACID PRODUCTION CAPABILITY

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Lactic acid bacteria (LAB) and their postbiotics demonstrated health benefits. GABA is an inhibitory neurotransmitter and crucial to the nervous system; it binds to the GABAergic system containing specific receptors. Dysfunctions in GABAergic receptor system have been associated with neurological diseases such as mood disorders, autism, depression, Alzheimer's disease, Parkinson's disease. Furthermore, several studies also linked beneficial effect of GABA on mood and sleep disorders, depression, cardiovascular diseases. Gut microbiota can indirectly regulate GABAergic neurotransmission *via* the vagus nerve. Beneficial microbes e.g. probiotics can modulate Gut–Brain Axis.

Therefore, the objective of the study is to formulate fermented milk beverage with antioxidant activity enriched with GABA. The 300 LAB strains isolated from Turkish artisanal fermented foods were screened for their ability of GABA and proteolytic activities. GABA concentrations of 33 strains in M17 and MRS broth media were determined by RP-HPLC using PITC derivatization. The degree of hydrolysis were quantified by OPA method in skim milk for 15 preselected strains having high proteolytic activity. The co-culture of LAB has been established based on the preliminary studies e.g. pH, reduction time of both single and co-cultures for their acidification behavior. Fermented milk was produced with %2 inoculum of *L. lactis* ssp. *lactis* and *Lactobacillus delbrueckii* ssp. *bulgaricus* and incubated at 37oC for 48 h and rapid decrease was observed through the pH value of 4.5. Fermented milk monitored at 0, 12, 24 and 48 h and analyzed for GABA content, degree of hydrolysis as L-leucine equivalent, antioxidant activity, pH decrease and viable cells. It can be envisaged that these strains can exert potential usage as starter cultures for manufacturing of functional foods & beverages.

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ESTABLISHMENT OF A DIRECT MEASUREMENT METHOD OF STOOL CONSISTENCY

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Background

Stool consistency is evaluated mainly using indirect indicators such as water content or the appearance of stool forms using Bristol Stool Form Scale (BSFS), but these methods are limited. We aimed to develop a simple protocol for direct measurement of stool consistency using the TA.XTExpress Texture Analyser (Stable Micro Systems Ltd.)

Methods

We developed a protocol which enables mechanical quantification of the gram-force against a cylindrical probe (ø 6 mm) pushed into the stool surface at 2.0 mm/s to 5 mm depth. The consistency of 252 stools collected from 40 healthy Belgians was evaluated by the direct method and by the indirect indicators (water content and BSFS).

Results

The log-transformed stool consistency values measured by the texture analyser had a negative linear correlation with the stool water contents (r_{rm} = -0.781) with homoscedastic variance, suggesting the appropriateness of the new protocol. They showed a similar correlation with the BSFS, but with a large variance in the consistency values of normal stool forms. This correlation was much smaller for BSFS scored by subjects (r_{rm} = -0.587) than by an expert (r_{rm} = -0.789), indicating BSFS as a rough indicator of stool consistency susceptible to subjective bias despite its effectiveness in clinical use.

Conclusions

The optimized direct method using the texture analyser enables the accurate quantification of stool consistency, which facilitates understanding of the intestinal environment and function and thus may enhance the value of the stool as a predictor of human health.

Funding and conflict of interest

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RESISTOME AND XENOBIOME TEMPORAL DYNAMICS IN POULTRY PRODUCTION CHAIN: THE CIRCLES PROJECT

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Background

The CIRCLES project aims to discover and translate innovative microbiomes-tailored circular actions into concrete applications that will ultimately enhance the EU food system performance, safety and sustainability. In the CIRCLES context, real-world labs in the fields for poultry food systems were created, allowing to increase knowledge on the importance of microbiomes in this food system. Specifically, we focused on the xenobiome and resistome, and their spread from farm to workers and environment, as microbiome functionalities to provide resistance to xenobiotics and antibiotics.

Methods

A total of 199 poultry feces, 13 samples from workers (skin and stools) and 70 environmental samples (boot soles, farm walls, lab coat surface, water, wastewater, air and soil) were collected at 3 time points from poultry production sites. DNA was extracted and sequenced by shotgun metagenomics, yielding a total of ~3.3 billions reads (total sequencing depth ~1 Tbp). Sequences were analyzed by HUMANn3 and Metawrap. Xenobiotic-degrading genes and antibiotic-resistance genes were recruited and used for the characterization of the xenobiome and resistome of the microbiomes.

Results

Beside the reconstruction of the compositional and functional dynamics of the animal gut microbiome in the poultry production cycles, we were able to reconstruct the temporal dynamics of the respective gut xenobiome and resistome, also highlighting the connections with those of workers and the environmental ones and the importance of a *Lactobacillus*-centered gut microbiome for poultry health.

Discussion and Conclusion

According to our preliminary findings, in the poultry production chains, xenobiome and resistome evolve over time and across the different ecosystems, with changes in complexity and diversity, showing specific patterns. This study paves the way to new microbiome-based intervention on poultry to minimize environmental impact and maximize food production.

Funding

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Conflict of interest

None.

FASTING AND FASTING MIMETIC SUPPLEMENTATION ADDRESS MICROBIOTA, METABOLITES, SIRTUIN EXPRESSION WITH EVIDENCE FOR AN INTERACTION OF MICROBIOTA WITH SIRTUIN EXPRESSION

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Background

Periodic fasting (PF) is an increasingly popular approach that assists in the management of metabolic and inflammatory diseases as well as in preventing mechanisms involved in aging. Fasting and fasting mimetics - bioactive compounds mimicking fasting effects, are of growing interest as potential means to slow down the aging process, cellular senescence and increase health span. Sirtuins (SIRTs) are known as enzymes that interfere with mitochondrial energy metabolism and molecular pathways involved in longevity. Sirtuin activating nutraceuticals are believed to mimic the effects of nutrient deprivation, thus activating signaling pathways correlated to an improved health span.

Objective

In this study, we compare 5 days periodic Buchinger fasting intervention with 3 months shot supplementation, a drink formula, containing secondary plant ingredients considered to activate sirtuins.

Methods

We analyzed pathways in response to fasting and a sirtuin activating drink containing mainly Gallic acid, EGCG, Phloretin, Anthocyanin, anthocyanidins, Oleuropein, Sulforaphane. Epigenetic biomarkers including telomere length, LINE1 methylation, and a set of mRNAs and miRNAs were assessed using qPCR analysis. Gut composition and metabolites were compared using Illumnia sequencing (Biomes) and mass spectrometry.

Results

A significant change in the gut composition was measured. Actinobacteria increased in the supplementation group, whereas after Buchinger fasting a rise in the distribution of Proteobacteria could be observed. After both interventions diversity increased and Firmicutes/Bacteroidetes ratio decreased and correlated with the body mass index (BMI). The abundance of longevity related *Christensenella* species increased after fasting and inversely correlated with age as well as body mass index (BMI). Fasting increased ketogenesis significantly. Fasting, but also the fasting mimetic could increase expression of FoxO1, SIRT1, and MLH1 mRNA, all genes discussed in aspects of longevity. A positive correlation between telomere length and both SIRT1, and SIRT6 and a correlation of the abundance of typically butyrate-producing Bacteroidetes with sirtuin regulating Mir125, siRT-1 expression, telomere length was observed.

Conclusions

Our results confirm the effects of fasting and Sirt activating drink on health and suggest an interaction between microbial metabolites and SIRTs.

We declare no conflict of interest

Reference

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BERRIES-GUT MICROBIOTA INTERACTION AND IMPACT ON HUMAN HEALTH: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

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Berries represent an important source of bioactive compounds, among which, (poly)phenols play a relevant role in mediating the modulation of gut microbiota and human health. Moreover, gut microbiota composition constitutes an important feature in the modulation of (poly)phenols metabolism and their biological effects. The aim of the current study is to assess data on the interaction of berries with gut microbiota, the production of phenolic and microbial metabolites, and the contribution to human health. A systematic review of randomized clinical trials present on PubMed and Scopus has been performed until July 2022. Data extraction includes study design, intervention details and the effect on main outcomes. The PRISMA guidelines and the Cochrane Risk of Bias tool have been used. PROSPERO database has been adopted for registering this systematic review (CRD42022336908). A total of 16 studies have been included. Concerning the modulation of the microbiome composition through the intake of berry, the findings have shown no change in overall microbiome diversities. Although, alpha diversity and beta-diversity did not show differences during the treatment with berries, at the single taxa level, the results showed common differences after treatment with berries intake. The most changed bacteria belonging to the genus Bifidobacterium was found to increase after berries intake. It has also been found an evident increase in SCFA-producing bacteria after the consumption of cranberry juice, in particular butyrate producers such as Eubacterium, Flavonifractor, and Subdoligranulum. Regarding genus correlated with the enzymes involved in flavonoid degradation, it has been observed an increase in Flavonifractor and Eggerthella after cranberry assumption. Also, Lactobacilli species, such as L. plantarum, Lacticaseibacillus casei, and Lactobacillus acidophilus, able to metabolize tannins, were found significantly increased after lyophilized jucara intake. In conclusion, berries, mainly through their content in (poly)phenols, could represent an important dietary component capable to modulate the composition and the function of intestinal microbes. In its turn, the gut microbiota catabolizes phenolic compounds to release bioactive metabolites that can impact both commensal microbiota and host health.

Funding and/or conflict of interest: none.

SINGLE STRAIN VS MULTI-STRAIN PROBIOTIC BACTERIA SUPPLEMENTATION ON IMMUNE PROFILE OF PEOPLE LIVING WITH HIV

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Introduction

HIV infection leads to intestinal microbial dysregulation, including reduced beneficial flora and increased pathogenic bacteria, and to disordered immune response characterized by imbalance of differentiation between innate and adaptive immune cells and of pro-inflammatory and anti-inflammatory cytokines, resulting in chronic inflammation. Abnormal gut microbiota also hinders the effect of antiviral therapy and affects the immune reconstruction of patients.

Methods

Patients clinically stable and virologically suppressed, without opportunistic infections and no ART changes in 12 months before the study started were enrolled and divided into 2 groups received for four weeks commercially-available: 1) multi-strain probiotics and 2) probiotic fermented milk drink containing *Lactobacillus casei* Shirota (*Lc*S).
Plasma viral load was determined using the Amplicor method, the numbers of T-cell subsets were determined by flow cytometry, and serum IL-10 were quantified using specific ELISA assays, according to the manufacturer's instructions

Results

No significant differences were found in the mean serum concentrations of principal metabolic parameters and indices of liver and kidney functions.
The numbers of T lymphocyte subpopulations useful for evaluating the immune response have been estimated in relation to the probiotic supplementation, and comparison of baseline measurements to those taken four-week showed a not significant increase of CD4+ and CD8+ cell after both *Lc*S and multi-strain probiotics intake, although greater with multi-strain probiotics.
Serum levels of IL-10 were not significantly changed after *Lc*S, while a significantly increased was detected after multi-strain probiotics.

Discussion

Our results suggest the same role of multi-strain probiotics and *Lc*S in the modulation of T cells subpopulation. IL-10, considered a broad effector molecule in immunoregulation/host defense, showed higher levels in serum of patients that received a multi-strain probiotics showing greater efficacy. However, this preliminary comparative study has some limitations, including a small sample size that could contribute to a lack of statistical significance for some parameters.

Conclusion

Waiting to definitively clarify the impact and mechanism of intestinal microbial dysbiosis on HIV immune escape and the impact of immune escape on immune reconstitution, the implementation of the diet with probiotics is a strategy that improves the quality of life of people who live with HIV.

No conflict of interest.

PROBIOTICS FOR THE MANAGEMENT OF INFECTIOUS DISEASES: REVIEWING THE STATE OF THE ART

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Background

Maintaining and potentially restoring the microbiota of humans is considered a vital aspect of health, protecting against many infectious and inflammatory diseases. Considering the rise of emerging infectious diseases like COVID-19, microbiota targeting interventions such as probiotics could be of great value to combat infectious diseases. The potential of probiotics as a clinical modality was investigated by creating an overview of the state of the art of research and development efforts as shown by patents and clinical trials since 1999.

Methods

Data were retrieved from patent and clinical trial databases to reflect the long- and short-term developments of probiotics research. The data were analyzed to extract information on the total number of patents and clinical trials for each indication, application date and location, and applicant/sponsor type.

Results

A total of 80 infectious diseases were investigated, precipitating in 789 patents and 602 clinical trials for 67 indications studied as targets of probiotic based interventions. An increasing trend was seen for the number of patents and clinical trials per year, with the highest number of patents and clinical trials targeted to digestive tract, respiratory, and urogenital indications.

Discussion and conclusion

Overall, research demonstrated a substantial interest in probiotics targeting infectious diseases, which was in line with reported unmet needs and global probiotics market estimates. However, a declining rate of translation from patents to clinical trials was observed. This could indicate that there are some barriers obstructing the research process, which may be detrimental to probiotic innovation.

Funding/conflict of interest

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THE GUT MICROBIOTA: MASTER OF PUPPETS CONNECTING THE EPIDEMIOLOGY OF INFECTIOUS, AUTOIMMUNE, AND METABOLIC DISEASE

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Background

Infectious, autoimmune, and metabolic diseases put an enormous pressure on both quality of life and the economy. For all three disease types, it is known that the quality of the gut microbiota composition is correlated to both onset and progression of disease. As such, the epidemiological trends of these disease types may serve as proxies for the integrity of the human gut microbiota.

Methods

Incidence data were retrieved from different public sources regarding prototypical infectious diseases (tuberculosis and measles), autoimmune disorders (type-1 diabetes and multiple sclerosis), and the prevalence of metabolic syndrome. The presented data covered incidences and vaccination coverage in 7 Western countries (Finland, France, Germany, Italy, the Netherlands, the United Kingdom and the United States) from 1980 until now.

Results

It was revealed that prototypical autoimmune disease incidence and metabolic disorder prevalence are still steadily increasing. This is accompanied by a plateauing decline in prototypical infectious disease incidence. Moreover, the data show a strong association between the level of eradication of infectious disease and the population coverage of vaccination programs.

Discussion and conclusion

The findings of this study suggest that the status of the gut microbiota is deteriorating, as reflected by the proxies. The epidemiological trends that were studied may serve as a starting point for a mechanistic understanding of the interplay between these different disease types that can be used for future prevention and mitigation strategies such as targeted stimulation and suppletion of microorganisms by means of, e.g., fermented foods, prebiotics and probiotics.

Funding/conflict of interest

O.F.A Larsen is also Senior Manager Science at Yakult Nederland B.V.

THE GUT MICROBIOTA AND IMMUNE RESPONSES IN COLORECTAL CANCER - A CHALLENGING TRIADE

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Colorectal cancer (CRC) develops at the interface between the host and the intestinal microbiota. Consequently, the gut microbiota has gained high attention in the field of onco-immunology. Insight in the mechanisms of the interaction between three extremely complex, constantly evolving, biological entities - microbiota, tumor cells and immune system - could fundamentally change therapeutic strategies of CRC patients and improve personalized cancer therapies in the near future. In a mouse model for colorectal cancer, we identified that within the tumorous tissues, hypoxia supports the perturbation of a suppressive microenvironment, as low oxygen availability in the tumorous tissue contributed to reduced CD4+ effector T cell functions and enhanced Treg suppression. Concurrently, specific microbial strains might benefit from these strong hypoxic conditions. We found changes in the Firmicutes/Bacteroidetes (F/B Ratio) in the feces of mice suffering from colorectal cancer. In addition, cancer-associated bacteria induced the secretion of pro-inflammatory cytokines by *in vitro*. Manipulation of the gut microbiota by antibiotic treatment of cancer-bearing mice kept intestinal tumorigenesis in check, most likely through changes in pro-inflammatory cytokine secretion. Indeed, chronic inflammation has been implicated in the initiation and progression of colorectal cancer. *Streptococcus gallolyticus* (*S.gallolyticus*) has been reported as one of the risk factors for CRC and was reported to have high pro-inflammatory potentials. Interestingly, we found that mediators of *S. gallolyticus* repress the secretion of CXCL10 of human colon cancer and immune cells in vitro and thus, could reduce the anti-tumorigenic potential of CD4+ and CD8+ T cells. In future, we aim to determine the specific molecular features of those pro-tumorigenic mediators of *S. gallolyticus*, which could pave the way for new (bacterio-) therapies in CRC.

AN IN-DEPTH ANALYSIS OF THE DECISION-MAKING PROCESS OF HEALTH CARE PROFESSIONALS; CONSIDERATIONS OF DIETICIANS AND GENERAL PRACTITIONERS TO RECOMMEND DAIRY AND PROBIOTICS IN THEIR PRACTICES

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Currently, a variety of foods such as probiotics and dairy are gaining substantial attention due to nutrition and therapeutic potential. Despite this therapeutic potential, little is known about health care professionals considerations to advise these food interventions in their practices. Therefore, this article explores the considerations health care professionals have to advise probiotics and dairy and how this relates to their actual advising behaviour. To this end, interviews were conducted with dieticians and general practitioners to identify the considerations that played a role in recommending dairy or probiotics. Subsequently a questionnaire was developed to collect quantitative data on the relation between the identified considerations and their actual advising behaviour, as well as on other advising behaviour specifications such as product choice. This paper showed that the advising behaviour of general practitioners regarding probiotics and dairy is the result of a multitude of interconnected considerations. These considerations did not rely exclusively upon explicit knowledge such as guidelines and evidence as obtained by RCTs but also upon implicit knowledge such as GPs recurring own observations regarding patients benefitting from the use of an intervention. Moreover, some considerations appeared to be only significantly related to the dairy survey such as the belief that dairy belongs in a healthy diet, whereas for the probiotic survey, GPs advising behaviour was primarily determined by their own and patients interest in probiotics. Finally, we find that dieticians in general perceive to have more knowledge and are more convinced of both their decision to (not) advise and regarding their product choice.

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Conflict of Interest
L.H.M. van de Burgwal is consultant for several commercial parties in the field of probiotics and life sciences; none of her advising practices conflict with the content of this research.
O.F.A Larsen is also Senior Manager Science at Yakult Nederland B.V.

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