



TARGETING MICROBIOTA

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International Society
of **microbiota**

RIKEN

2ND
CONJOINT
MEETING

SCIENTIFIC ABSTRACTS 2026

Oral Communications

Short Talks

Posters

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ISM - RIKEN TARGETING MICROBIOTA 2026

TOKYO
JAPAN
2026

2ND
CONJOINT MEETING

International Society of Microbiota

September 24-25, 2026 – Tokyo, Japan

Hiroshi Ohno

President of Tokyo Targeting Microbiota 2026

Alain Stintzi

President, International Society of Microbiota

Soheil Saeedi

Vice-President, International Society of Microbiota

Marvin Edeas

Founder and Chairman of ISM Scientific Committee

This meeting is part of the RIKEN Symposium Series.

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Welcome to the Second Conjoint Meeting of RIKEN-ISM

Dear Colleagues and Friends,

It is a great pleasure to welcome you to The University of Tokyo for the Second Conjoint RIKEN-ISM Targeting Microbiota Meeting.

Over these two days, scientists, clinicians and innovators from Japan and around the world come together around a central question: how can we move microbiota science from observation to mechanism, and from mechanism to meaningful intervention?

This is the scientific ambition of Tokyo Microbiota 2026.

Day 1 explores how we understand and measure the microbiome, from host-microbiota dialogue and microbial metabolites to single-cell and strain-level resolution.

Day 2 moves from function to intervention, with particular attention to the microbiota-mitochondria axis, healthy aging, precision microbiome medicine, next-generation therapeutics and innovation. This progression is already reflected in the scientific structure of the program.

Beyond the lectures, we hope this meeting will create space for discussion, new collaborations and unexpected scientific connections. The diversity of disciplines represented here is essential if microbiota research is to move toward causality, precision and clinical impact.

We thank all speakers, chairs, researchers, partners and participants who have travelled to Tokyo and contributed to making this meeting possible.

We also wish to thank the supporters: *Morinaga*, *Ecyte*, *Nature Portfolio*, *Yakult*, and *Japan Eco-science Co., Ltd.*

International Society of Microbiota Leadership

Prof. Alain Stintzi

President, International Society of Microbiota
University of Ottawa, Canada

Prof. Soheil Saeedi

Vice-President, International Society of Microbiota
University of Zurich, Switzerland

Welcome to Tokyo. We wish you two stimulating and productive days of science and exchange.

Prof. Hiroshi Ohno

RIKEN Center for Integrative Medical Sciences, Japan
President, Tokyo RIKEN-ISM Targeting Microbiota 2026

Prof. Marvin Edeas

Institut Cochin, Université Paris Cité, France
Chairman of the ISM Scientific Board

Thanks to Our Speakers & Supporters



MASAYUKI AMAGAI

Opening Remarks:
2nd Conjoint RIKEN-
ISM Targeting
Microbiota 2026



HIROSHI OHNO

Concluding Remarks:
2nd Conjoint RIKEN-
ISM Targeting
Microbiota 2026



MARVIN EDEAS

The Microbiota Sends
the Signal. Do
Mitochondria Decide the
Response?



YOSHIHAZU NAKAOKA

Gut Microbes,
Tryptophan Metabolism,
and Pulmonary
Hypertension:
A Targetable Gut-Lung
Axis



YUMI MATSUOKA

From Quorum-Sensing-
Driven Pathogenesis to
Microbiome: Targeted
Therapies in Atopic
Dermatitis



PATRICK C.H. HSIEH

Microbiota-Metabolite
Control of Cardiac Injury
and Repair



GENE TYSON

Single-Cell Visualization
and Australia's Human
Microbiome Biobank:
New Tools for Strain-
Level Microbiome
Science



JIAN XU

Single-Cell
Ramanomics Platform
Enables Rapid Probiotic
Quality Assessment and
Strain Traceability



YUMA YAMADA

Engineering Mitochondrial
Stress Tolerance through
Mitochondria-Targeted
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on the Microbiota-
Mitochondria Axis



WATARU SUDA

Strain- and Function-
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Identify Microbial
Drivers of Chronic
Disease



GWANGPYO KO

Development of Smart
Biodelivery Systems for
Personalized Disease
Treatment Based on the
Gut Microbiome



REIKO SHINKURA

Can IgA Reprogram the
Human Gut Microbiota
in Inflammatory Bowel
Disease?



ELISA HILL-YARDIN

When Synapses Shape
the Microbiome:
Decoding the Gut-Brain
Axis in Autism



NAOKO SATOH-
TAKAYAMA

Microbial Metabolites as
Drivers of Gastric
Mucosal Defense



SIN-HYEOG IM

Precision Microbiome
Therapeutics to
Enhance Cancer
Immunotherapy



IPPEI SHIMIZU

The Microbiota-Muscle
Axis in Aging: How
Trimethylamine N-Oxide
(TMAO) Remodels
Mitochondria and
Promotes Sarcopenia



DONGRYEOL RYU

Living Probiotics,
Microbial Metabolites,
and Mitochondrial
Resilience: A Pathway
to Healthy Aging



DINGBO LIN

Carotenoid Metabolism
Regulates the
Microbiota-
Mitochondria Axis: From
Diet to Single-Cell
Heterogeneity



MASAHITO HOSOKAWA

From Strain Diversity to
Mobile Element
Dynamics in Human
Microbiomes with
Single-Cell Genomics



TAKUJI YAMADA

Resolving Microbial
Drivers of Colorectal
Cancer:
From Population
Signatures to Strain-
level Resolution and
Mutational Footprints



SAWAKO HIBINO

Exosome-Microbiome
Crosslink Across the
Gut-Liver Axis as a Key
Mechanism Supporting
Estrogen Homeostasis
and Metabolic Balance

nature
portfolio

Yakult



eCcyte



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DOI Information

The Tokyo Targeting Microbiota 2026 Abstracts Book has been assigned a Digital Object Identifier (DOI), providing a permanent and citable record of the scientific contributions presented during the meeting.

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How to Cite Your Abstract

Example:

Furuya G, Usui F, Takahashi K, et al. Cross-species reactive IgA balances pathobionts and beneficial commensals via physicochemical pattern recognition. Tokyo Targeting Microbiota 2026 Abstracts Book. 2026; p.15. doi: 10.60738/3cgw-0884.



Practical Information

We would like to take the opportunity to give you some additional information about the meeting arrangements.

The Abstract book contains:

- Speakers' abstracts (the abstracts of the oral presentations follow the order of the program)
- The abstracts of posters on display

Badges

Upon registration you have received your own personal badge. Please wear this badge during the entire meeting including the coffee breaks and lunch.

The conference secretariat will be in the area in front of the conference hall.

Instructions for participants

Chairpersons: The Chairpersons will be seated at the president's table.

Speakers: Speakers are invited to give their Power Point presentations for downloading on the computer to the technical team outside and not inside the conference hall. As the schedule is rather tight and to allow sufficient time for discussions, we would be very much obliged if the timing requirements were respected.

Poster Contributors: Please ensure that your poster is displayed at the appropriate location, please respect your poster number. Please remember to remove your posters at the end of the conference. The Poster contributors are invited to stand by their poster during the poster sessions.

Mobile Phones

As a courtesy to the speakers and other delegates, please turn off your mobile phones or to silent whilst in the conference room. Please do not take pictures of the slides without the consent of the presenting author.

Questions

Please state your name and institution or company before asking your question.

Conference Staff

Staff at the conference registration desk will be happy to deal with any queries you may have. If we receive any messages for you, they will be announced at the break in the session and can be collected from the desk.

Personal Belongings

Please keep your valuables and working materials with you at all times. We would advise you to keep your name on the conference notes, as we may not be able to replace these if lost. The ISM and The University of Tokyo can't be held responsible for any loss or damage to your property.

Second Conjoint Meeting of RIKEN-ISM

Tokyo Targeting Microbiota

September 24-25, 2026
Tokyo, Japan

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Second Conjoint Meeting of RIKEN-ISM

Tokyo Targeting Microbiota

Abstracts of Day 1

September 24, 2026



OPENING REMARKS: 2ND CONJOINT RIKEN–ISM TARGETING MICROBIOTA 2026

AMAGAI, Masayuki

Center Director, RIKEN Center for Integrative Medical Sciences (IMS), Japan



Prof. Masayuki Amagai, MD, PhD, Director of the RIKEN Center for Integrative Medical Sciences and Professor of Dermatology at Keio University School of Medicine, will deliver the opening remarks at the 2nd Joint RIKEN–ISM Targeting Microbiota 2026, taking place on September 24–25, 2026, at The University of Tokyo.

CAN IGA REPROGRAM THE HUMAN GUT MICROBIOTA IN INFLAMMATORY BOWEL DISEASE?

SHINKURA, Reiko

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Dr. Reiko Shinkura, Professor at the Institute for Quantitative Biosciences at the University of Tokyo, will deliver the keynote presentation at the RIKEN-ISM Targeting Microbiota 2026, unveiling a bold new approach to treating gut dysbiosis: orally administered IgA antibodies that selectively reshape the gut microbiome.

Where conventional antibiotics destroy beneficial bacteria alongside pathogens, triggering recurrent disease, Dr. Shinkura's mouse-derived multimeric IgA antibody takes a smarter path: it suppresses harmful bacteria while leaving beneficial species like lactic acid bacteria and butyrate producers intact. This preserves the gut's natural colonization resistance rather than dismantling it.

Her team has demonstrated that oral IgA administration effectively restores microbiota balance in mice colonized with IBD patient-derived microbiota, not by targeting a single pathogen, but by regulating the entire microbial ecosystem. This whole-community approach positions IgA therapy as a potential therapeutic strategy, fundamentally distinct from current treatments like fecal microbiota transplantation or single-target antibiotics.

In this keynote, Dr. Shinkura will make the case for IgA antibody therapy as a transformative new class of microbiota medicine, one that could redefine how we treat inflammatory bowel disease and dysbiosis-driven conditions.

GUT MICROBES, TRYPTOPHAN METABOLISM, AND PULMONARY HYPERTENSION: A TARGETABLE GUT–LUNG AXIS

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Dietary tryptophan is an essential host nutrient and a substrate for intestinal microbes. Host epithelial absorption limits microbial access, whereas microbial metabolism generates indole derivatives (indoles) that can activate the aryl hydrocarbon receptor (AHR), a regulator of barrier and immune function. Whether disruption of this nutrient partitioning leads to excess pathogenic metabolites and drives disease beyond the gut is unknown. We investigated this question in pulmonary arterial hypertension (PAH), a fatal vascular disease in which AHR activation promotes inflammation and remodeling (Masaki et al., PNAS 2021; Asano et al., under revision). Here we show that PAH is sustained by a self-amplifying intestinal circuit linking gut dysbiosis, impaired tryptophan absorption, and excess production of AHR-activating indoles. In a patient cohort enriched for PAH, ectopic oral bacteria and expansion of bacteria A were associated with increased fecal indoles, intestinal AHR activity, and poor outcomes. Gnotobiotic, pharmacological, and genetic studies have shown that microbiota-derived indoles exacerbate pulmonary vascular remodeling via AHR signaling. Therapeutically, the intestinal adsorbent substance-X interrupted this circuit and attenuated disease. These findings identify intestinal nutrient partitioning as a targetable gut-lung mechanism that converts dysbiosis into distal vascular pathology, namely PAH.

WHEN SYNAPSES SHAPE THE MICROBIOME: DECODING THE GUT–BRAIN AXIS IN AUTISM

HILL-YARDIN, Elisa

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Prof Elisa Hill-Yardin, a prominent neuroscientist at RMIT University in Melbourne and a member of Australia's inaugural Profound Autism Advisory Committee. She has a notable history of advocacy, including campaigns that have resulted in legislative changes locally and internationally for people with autism and brain disorders. Prof. Hill-

Yardin will present her research on how the gut-brain-microbiota axis influences gastrointestinal dysfunction in autism.

Her research has revealed that autism-associated variants in the synaptic gene neuroligin-3 don't just alter brain connectivity; these changes fundamentally alter enteric nervous system function, modifying gut motility, mucosal barrier integrity, and immune cell behavior. Strikingly, mice expressing the neuroligin-3 R451C variant exhibit fecal microbial dysbiosis even in shared housing environments, providing evidence that the nervous system itself regulates gut microbial populations.

These findings point to a bidirectional loop where gene variants encoding synaptic proteins reshape the gut environment, altering microbial communities and neuro-immune signaling. Prof Hill-Yardin will discuss how these insights are informing new directions in personalized microbial therapies, microbiome engineering, and mucosal barrier optimization, in particular for individuals living with profound autism and other neurological conditions.

From Quorum-Sensing-Driven Pathogenesis to Microbiome - Targeted Therapies in Atopic Dermatitis

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Atopic dermatitis (AD) is associated with dysbiosis of the skin microbiome, particularly colonization by *Staphylococcus aureus*. However, whether *S. aureus* acts as a pathogenic driver or a relatively benign colonizer depends on how its virulence is regulated within the skin environment. The accessory gene regulator (Agr) quorum-sensing (QS) system plays a central role in controlling virulence gene expression, linking bacterial communication to host–microbe interactions. Our recent study suggests that Agr activity is shaped by ecological and evolutionary dynamics, including nutrient availability and inter-strain competition, leading to the emergence of non-producing “cheater” variants. These dynamics can shift bacterial populations toward reduced virulence states, indicating that pathogenicity is not fixed but context-dependent. In this talk, I will discuss how QS-mediated regulation of *S. aureus* integrates with host immunity to determine disease outcomes in AD. I will further highlight emerging microbiome-targeted therapeutic strategies, including ecological modulation and quorum-quenching approaches, and discuss their potential for preventive and therapeutic applications.

GLOBAL GRANTS FOR GUT HEALTH: CONNECTING MICROBIOME SCIENCE WITH GLOBAL FUNDING OPPORTUNITIES

Nature Portfolio & Yakult

Nature Portfolio, Yakult and ISM Join Forces in Tokyo to Connect Global Funding with Japanese Microbiome Research

From Japanese Microbiome Science to Global Opportunity

A new opportunity is opening for the microbiome research community in Japan.

On 24–25 September 2026 at The University of Tokyo, ISM–RIKEN Targeting Microbiota will welcome the Global Grants for Gut Health (GGGH) programme, jointly supported by Nature Portfolio and Yakult.

GGGH has already supported more than USD 2.5 million in microbiome research and awards three research grants of USD 100,000 each year.

In Tokyo, the programme will be presented directly to Japanese and international researchers, with a dedicated presentation explaining its objectives, impact and application process.

How can Japanese microbiome research connect more strongly with global funding?

The discussion will bring together Hiroshi Ohno, RIKEN Center for Integrative Medical Sciences; Kiyoshi Takeda, Osaka University; Reiko Shinkura, The University of Tokyo; and Yumi Matsuoka, Osaka University, together with Jeffrey Robens from Nature Portfolio.

They will be joined by Marvin Edeas, Founder and Chairman of ISM, to explore how Japanese researchers can engage more effectively with international funding opportunities.

Three Best Abstract Prizes in Tokyo: JPY 100,000 each

The collaboration also introduces: Three Global Grants for Gut Health Best Abstract Prizes

The recipients will be selected by the conference scientific and organising committees, keeping scientific excellence and independence at the heart of the awards.

Beyond funding, ISM–RIKEN Tokyo will bring together leading Japanese and international scientists for two days spanning host–microbiota interactions, microbial metabolites, gut–brain and gut–lung communication, single-cell and strain-level approaches, precision therapeutics and emerging microbiome technologies.

The objective is clear: to create stronger connections between Japanese scientific excellence, international collaboration and new opportunities for the next generation of microbiome researchers.

MICROBIOTA-DEPENDENT BILE ACIDS REGULATE ALVEOLAR MACROPHAGE AND FIBROBLAST IMMUNOMETABOLISM TO PROTECT AGAINST ALLERGIC AIRWAY INFLAMMATION

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Crosstalk between the gut and lungs in shaping pulmonary immunity is increasingly recognized, yet the contribution of gut microbiota-derived metabolites remains poorly understood. Here, using mouse models of allergic airway inflammation, mechanistic studies in human primary cells, and metabolomic profiling of bronchoalveolar lavage fluid from patients with asthma, we identify a microbiota-bile acid-lung axis that constrains type 2 inflammation. The lithocholic acid pathway was depleted in obese patients with asthma, a clinical phenotype associated with increased disease severity. In mice, boosting this pathway by intranasal administration of isolithocholic acid (isoLCA) or oral delivery of a rationally assembled bacterial consortium attenuated allergic airway inflammation. Mechanistically, consistent with our previous findings, isoLCA reprogrammed alveolar macrophage immunometabolism and, unexpectedly, also acted on pulmonary fibroblasts through a vitamin D receptor- and oxidative phosphorylation-dependent mechanisms. Together, these findings establish the lithocholic acid pathway as a tractable therapeutic target for asthma.

CROSS-SPECIES REACTIVE IGA BALANCES PATHOBIONTS AND BENEFICIAL COMMENSALS VIA PHYSICOCHEMICAL PATTERN RECOGNITION

FURUYA, Genta (1); USUI, Fumihito (2); TAKAHASHI, Keishu (1); TAMANO, Ryutaro (1); SASAKI, Kengo (1); MORITA, Naoki (1); GAO, Peng (1); SHINKURA, Reiko (1)

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Mucosal immunity uniquely orchestrates symbiosis with non-self bacteria. Immunoglobulin A (IgA) regulates the gut microbiome by inhibiting multiple pathobionts (cross-species reactivity) while preserving beneficial commensals. How cross-species reactivity and discriminative recognition coexist within a single IgA clone remains poorly understood.

Here, we demonstrate that a "cross-species reactive yet discriminating" IgA, W27, recognizes a conserved physicochemical pattern in pathobiont proteins and inhibits their folate cycle. W27 targets multiple pathobionts, including *Escherichia coli* and *Clostridioides difficile*.

W27 binds distinct bacterial proteins, namely serine hydroxymethyltransferase (SHMT) in *E. coli* and cofactor-independent phosphoglycerate mutase (iPGM) in *C. difficile*. X-ray crystallography reveals shared polar and non-polar amino acid motifs across SHMT from Gammaproteobacteria and iPGM from Peptostreptococcales. SHMT is a major surface antigen on membrane blebs. W27 inhibits its enzymatic activity, slowing folate-cycle flux and limiting proliferation. In gnotobiotic mice co-colonized with isogenic strains differing only in their SHMT epitope (pathobiont-type vs. beneficial-type), W27 selectively suppressed the pathobiont-epitope strain, confirming epitope-specific microbiota editing *in vivo*.

These data reveal how mucosal immunity discriminates pathobiont non-self from beneficial non-self, and support monoclonal IgA as a therapeutic strategy for editing the gut microbiota.

This research was supported by AMED under Grant Numbers JP17gm1010008, JP243fa627001, JP22zf0127009 and JP25fk0210164, and by JST under Grant Number JPMJMS2214-17 (to R. S.) and by AMED under Grant Number JP223fa627001 (UTOPIA Young Researcher Development Program), JSPS KAKENHI Grant-in-Aid for Research Activity Start-up, the Mishima Kaiun Memorial Foundation, the Yakult Bio-Science Foundation, the Kenzo Suzuki Memorial Foundation for Applied Science, and the Takahashi Industrial and Economic Research Foundation (to G. F.).

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INTESTINAL EPITHELIAL AUTOPHAGY REGULATES GLUCOSE METABOLISM VIA THE GUT MICROBIOME

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Introduction: Autophagy maintains mucosal integrity and energy balance. Autophagy-related gene 9A (Atg9a), the only transmembrane protein within the autophagy-related members, is essential for autophagosome membrane expansion. Recently, Atg9a has been shown to exert non-canonical functions beyond classical autophagy, and its role in host metabolism remains poorly understood.

Materials & Methods: Intestinal epithelial-specific Atg9a knockout and control mice were evaluated on a standard chow diet and a high-fat diet (HFD). Phenotypic analyses included metabolic profiling, gut histology, and 16S rRNA sequencing. The microbial effects of Atg9a knockout microbiota were assessed using antibiotic-mediated depletion.

Results: Intestinal Atg9a deficiency induced epithelial hyperplasia and promoted secretory cell differentiation throughout the gut. The knockout mice exhibited elevated hepatic glycogen storage and showed resistance to HFD-induced obesity and insulin resistance. Microbial profiling revealed significant community remodeling and enriched Marvinbryantia in intestinal Atg9a-deficient mice. Antibiotic depletion abolished the glycemic improvements in intestinal Atg9a-deficient mice, indicating that glycemic control is specifically gut microbiota-dependent. Furthermore, supplementation with Marvinbryantia formatexigens directly improved glucose metabolism under high-fiber HFD feeding in conventional specific-pathogen-free mice.

Conclusion: Intestinal Atg9a regulates systemic glucose metabolism through microbiome remodeling. Targeting the intestinal Atg9a–Marvinbryantia axis offers a potential therapeutic strategy for obesity, insulin resistance, and diet-induced metabolic disorders.

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MICROBIAL METABOLITES AS DRIVERS OF GASTRIC MUCOSAL DEFENSE

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Prof. Naoko Satoh-Takayama, Unit Leader at the RIKEN Ecosystem and Coevolution Laboratory (ECL), Visiting Professor at Tokyo University of Science and Mie University, and Adjunct Associate Professor at Yokohama City University Graduate School, will discuss how innate lymphoid cells (ILCs) serve as rapid-response sentinels at mucosal surfaces, integrating dietary and microbiota-derived signals to calibrate immune homeostasis and prevent excessive inflammation.

Mucosal tissues face a constant immunological challenge: they must remain permeable for nutrient absorption and gas exchange while simultaneously defending against pathogens and tolerating commensal microorganisms and dietary antigens. Among the immune populations tasked with maintaining this balance, ILCs have emerged as critical early regulators, orchestrating downstream immune responses that shape tissue protection and repair.

During her talk, Prof. Satoh-Takayama will present recent advances in understanding how environmental factors such as dietary components and microbiota-derived signals directly shape ILC-mediated immune responses in mucosal tissues. She will address how these signals instruct ILC subset differentiation and function, and how disruption of this dialogue may contribute to the pathogenesis of immune-mediated diseases.

MICROBIOTA-METABOLITE CONTROL OF CARDIAC INJURY AND REPAIR

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Dr. Patrick C.H. Hsieh, a distinguished cardiovascular surgeon and physician-scientist specializing in regenerative medicine and bioengineering, will discuss how the gut-heart axis fundamentally reshapes our understanding of myocardial repair, revealing that cardiac responses to injury are governed not autonomously but through a complex cross-organ network driven by the gut microbiota and their derived metabolites.

The heart has long been viewed as self-governing in its response to damage. However, emerging evidence now establishes that dysbiosis and the loss of gut microbiota alter the systemic immune landscape, impairing post-infarction cardiac repair. At the center of this regulatory axis are microbial metabolites, particularly short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which act as key signaling molecules modulating immune-metabolic signatures.

During his talk, Patrick Hsieh will present evidence demonstrating how these metabolites confer cardiac protection, enhance adaptation to pressure overload, and create new therapeutic opportunities, including microbiota modulation to optimize the efficacy of cardiac cell therapy in non-human primates and to influence host responses to biomaterial implantation.

THE MICROBIOTA–MUSCLE AXIS IN AGING: HOW TMAO REMODELS MITOCHONDRIA AND PROMOTES SARCOPENIA

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Dr. Ippei Shimizu, a leader in cardiovascular science, will talk about how the gut microbiota-derived metabolite TMAO emerges as a critical age-associated factor linking metabolic dysregulation to mitochondrial remodeling and sarcopenia.

Building on his team's prior findings that TMAO is elevated in heart failure patients and induces mitochondrial dysfunction, metabolomic analyses now reveal that circulating TMAO levels increase with aging in both mice and humans. During his talk, he will present evidence that TMAO disrupts mitochondrial ultrastructure, independently of autophagy or endothelial senescence. Notably, TMAO infusion reduced running capacity in middle-aged mice, with skeletal muscle phenotypes mirroring those of aged animals, identifying TMAO as a mechanistic link between gut microbial metabolism and sarcopenia.

GUT MICROBIOTA MATURATION AND A MUCIN–AROMATIC-METABOLITE AXIS ARE ASSOCIATED WITH POSTNATAL GROWTH FALTERING IN PRETERM INFANTS

WENG, Yi-Hsiu (1,2); LIN, Yung-Chieh (3); HUANG, Chao-Ching (3,4); RUAN, Jhen-Wei (1,2)

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2: Department of Medical Laboratory Science and Biotechnology, National Cheng Kung University, Taiwan.;

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Introduction: Preterm infants are vulnerable to postnatal growth faltering, linked to gut microbiota maturation during neonatal intensive care.¹ Combining gut microbiota enterotyping with serum metabolomics in a rare periviable (22–25 weeks) cohort with paired longitudinal sampling, we linked the developing gut to growth.

Material & Methods: 170 preterm infants were enrolled and stool was collected at postmenstrual age (PMA) 30–31 weeks (n=152) and term-equivalent age (TEA; n=170) for fecal 16S rRNA (V3–V4) sequencing, and serum metabolomics (n=92).

Results: We identified three enterotypes in this cohort. Enterotype 3 had the lowest head-circumference Z-score at TEA ($P=0.0034$), was enriched among periviable infants, showed incomplete PMA-to-TEA maturation, and was predictable from the early microbiome ($AUC=0.69$). Unexpectedly, *Akkermansia* was associated with growth faltering and *Clostridium sensu stricto* 1 with better growth. Fecal MUC-2 was lowest in enterotype 3 ($P<0.001$) and inversely correlated with *Akkermansia* ($\rho=-0.34$); MUC-2 mediated the *Akkermansia*–body-weight association (ACME $P=0.008$; $\approx 25\%$ of the total effect), but not head circumference ($P=0.089$). Serum phenolic/tyrosine catabolites (p-cresol sulfate, 4-ethylphenylsulfate) were positively associated with *Akkermansia* and negatively with MUC-2, whereas tryptophan indoles showed the reverse.

Conclusion: An integrated microbiome–metabolite signature could estimate the growth-faltering risk of preterm infants, highlighting an early, modifiable intervention window.

Supported by National Science and Technology Council, Taiwan

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GUT ACIDIFICATION IMPAIRMENT LINKS ALTERED ACIDOGENIC MICROBIOTA TO INFANTILE ECZEMA: A CROSS-SECTIONAL STUDY

ZHENG, Huiwen (1); LI, Yin (1); LI, Wei (1); GUO, Xiaoxuan (1); HUANG, Chunlan (1); ZHOU, Sha (1); LI, Yunling (1); **ZHU, Liying** (2,3)

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Introduction: The infant gut microbiota is essential for immune development, yet its alteration in infantile eczema remains poorly understood [1]. We investigated taxonomic and metabolic differences between infants with eczema and healthy controls.

Material & Methods: Full-length 16S rRNA gene sequencing, qPCR, faecal metabolite measurements, and in vitro batch fermentation with different carbon sources were used to assess microbial composition, absolute bacterial abundance, metabolic activity, and substrate-dependent responses.

Results: Infants with eczema showed depletion of acidogenic and acidophilic taxa, including *Enterococcus faecium*, *Citrobacter*, and *Streptococcus* unclassified, together with lower absolute counts of *Lactobacillus*, reduced total bile acids, and altered short-chain fatty acid profiles. In vitro fermentation reproduced several group-specific differences, although their extent varied among substrates. *Escherichia-Shigella*, *E. coli*, *Citrobacter*, *Clostridium butyricum*, and the [Ruminococcus] gnavus group were more frequently enriched in controls. Notably, XYI fermentation significantly separated the eczema and control microbiota despite no significant β -diversity difference in the original faecal samples.

Conclusion: These findings link gut acidification impairment to altered acidogenic microbiota [2] in infantile eczema. We propose a Dual Driving Force Hypothesis in which early-life lactate accumulation and subsequent bile acid maturation [3] sequentially shape infant gut microbiota succession and may influence immune maturation.

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CAN GUT MICROBIOTA-DERIVED COBALAMIN PROTECT BONES IN POSTMENOPAUSAL WOMEN? THE MICROBONE STUDY

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Introduction: Individuals with vitamin B deficiency may have lower bone mineral density (BMD) and higher risk of osteoporosis. However, potential contribution of gut microbiota (GM)-derived B vitamins to BMD in older women remains unknown.

Material & Methods: We recruited 373 postmenopausal women aged ≥ 60 yr: 180 women with normal BMD and 193 women with osteoporotic BMD. GM metagenomic species were identified by using high throughput shotgun sequencing followed by the METEOR2 and MSPminer analyses. Metabolic modules were annotated using the KEGG, GBM and GMM databases.

Results: Two cobalamin (B12) synthesis modules (KEGG: M00924, M00122) were decreased in women with osteoporotic BMD vs. those with normal BMD. The osteoporotic group had lower occurrence and/or abundance of metagenomic species which carried both the modules, e.g., *Coprococcus comes*, *Megamonas funiformis*, *Anaerobutyricum hallii*, *Agatobaculum butyriciproducens*, *Agathobacter faecis*, *Dialister invisus*, *Dialister succinatiphilus*, *Dorea longicatena*, *Dorea formicigenerans*, *Mediterranea massiliensis*, *Klebsiella pneumoniae*. The modules of thiamin salvage pathway (B1) and of synthesis of riboflavin (B2), pyridoxal (B6), biotin (B7) and tetrahydrofolate (B9) were also lower in the osteoporotic group but the differences were less consistent.

Conclusion: In older women, osteoporosis (decreased BMD) may be partly linked to a reduced potential of the GM-mediated vitamin B synthesis, especially cobalamin.

The MICROBONE study was supported by a grant from the MSDAVENIR program.

SINGLE-CELL VISUALIZATION AND AUSTRALIA'S HUMAN MICROBIOME BIOBANK: NEW TOOLS FOR STRAIN-LEVEL MICROBIOME SCIENCE

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Prof. Gene Tyson, Director of the Center for Microbiome Research at Queensland University of Technology and Director of the Australian Human Microbiome Biobank, will discuss how strain-level resolution and mechanistic study of uncultured species can be achieved through an integrated platform that combines national-scale biobanking with single-cell visualization.

Most species detected in human-associated microbiomes have never been cultured, restricting functional work to computational inference, while sequencing-based methods recover compositional information but cannot localize individual strains or mobile genetic elements within complex communities. Prof. Tyson's laboratory has developed two complementary tools to address these challenges in tandem.

During his talk, he will present the Australian Human Microbiome Biobank (AHMB), a national research infrastructure housing over 25,000 authenticated, whole-genome sequenced microbial isolates from the human gut, skin, oral, and vaginal microbiomes, approximately 38% of which represent previously uncultured species, supported by a high-throughput anaerobic cultivation platform integrating spectral flow cytometry and metagenomics. He will then introduce GenomeFISH, a genome-based fluorescence in situ hybridization approach that achieves strain-level resolution at up to 99% average nucleotide identity. Extensions of this method, PlasmidFISH and VirusFISH, enable in situ localization of plasmids and bacteriophages within their host cells. This presentation provides the enabling technologies required to move from taxonomic cataloging to strain-resolved, mechanistic understanding of the human microbiome, a prerequisite for precision microbiota-based interventions.

FROM STRAIN DIVERSITY TO MOBILE ELEMENT DYNAMICS IN HUMAN MICROBIOMES WITH SINGLE-CELL GENOMICS

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Masahito Hosokawa, Professor at Waseda University and co-founder of bitBiome, Inc., will present how single-cell genomics is transforming our ability to decode strain-level complexity within human microbiomes and track the spread of antibiotic resistance.

The human microbiome harbors vast within-species diversity that shapes how resistance genes and mobile genetic elements move through microbial communities. Yet linking these elements to their specific bacterial hosts has remained a major challenge. Dr. Hosokawa's work solves this by applying high-throughput single-cell genome sequencing to recover strain-resolved genomes directly from gut and skin microbiomes, creating an unambiguous connection between mobile elements and their host bacteria.

He will introduce frameworks that integrate single-cell genomics with metagenomics and long-read sequencing, and present a single-amplified genome catalog that enables systematic characterization of mobilome and resistome dynamics across microbial communities.

This talk demonstrates how single-cell genomics moves microbiome science from broad community profiling to precise, strain-level biological insight, laying the groundwork for more targeted microbiome interventions.

SINGLE-CELL RAMANOMICS PLATFORM ENABLES RAPID PROBIOTIC QUALITY ASSESSMENT AND STRAIN TRACEABILITY

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Dr. Jian Xu, Founding Director of the Single-Cell Center at CAS-QIBEBT, a pioneer in single-cell metabolic phenomics and inventor of the Ramanomics Instrument Series, will discuss how a novel culture-free, single-cell-resolution strategy can transform the quality assessment of probiotics and live-cell products for the rapidly expanding industry.

Rapid expansion of the probiotics industry demands fast, sensitive, comprehensive, and low-cost strategies for quality assessment. Here, we introduce a culture-free, one-cell-resolution, phenome-genome-combined strategy called Single-Cell Identification, Viability and Vitality tests, and Source-tracking (SCIVVS). For each cell directly extracted from the composite probiotics product, the fingerprint region of D2O-probed single-cell Raman spectrum (SCRS) enables species-level identification with 93% accuracy, based on a reference SCRS database from 21 statutory probiotic species, whereas the C–D band accurately quantifies viability, metabolic vitality plus their intercellular heterogeneity. For source-tracking, single-cell Raman-activated Cell Sorting and Sequencing can proceed, producing indexed, precisely one-cell-based genome assemblies that can reach ~99.40% genome-wide coverage. Finally, we validated an integrated SCIVVS workflow with automated SCRS acquisition where the whole process except sequencing takes just 5 h, using the Raman Flow Cytometer that we invented (FlowRACS). As it is >20-fold faster, >10-time cheaper, vitality-revealing, heterogeneity-resolving, and automation-prone, SCIVVS is a new technological and data framework for quality assessment of live-cell products.

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RESOLVING MICROBIAL DRIVERS OF COLORECTAL CANCER: FROM POPULATION SIGNATURES TO STRAIN-LEVEL RESOLUTION AND MUTATIONAL FOOTPRINTS

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The gut microbiome has been repeatedly associated with colorectal cancer (CRC), yet identifying microbial signatures alone does not establish which bacteria actively contribute to tumorigenesis. Here, I will present our recent studies that progressively move from population-level microbiome signatures toward strain-level functional resolution and host genomic evidence of microbial exposure.

First, using integrated metagenomic, metabolomic, and quantitative PCR analyses of Japanese CRC cohorts, we identified microbial and metabolic features associated with early-onset CRC. These included disease-associated microbial species and functional factors such as virulence-related genes, highlighting the importance of resolving microbial functions beyond species level associations. In particular, colibactin-producing bacteria emerged as a potential contributor to early-onset CRC.

Second, to experimentally investigate the functional consequences of strain diversity, we isolated bacterial strains from patients with early-stage CRC. Clinical isolates of CRC-associated bacteria, including *Lancefieldella parvula*, *Schaalia odontolytica*, and *Solobacterium moorei*, showed genomic differences from reference strains, and administration of a cocktail of patient-derived strains enhanced tumorigenesis in a CRC mouse model. These findings demonstrate that disease-associated phenotypes can depend on the specific strains present within a microbial community.

Finally, by integrating whole-genome sequencing of CRC tumors with fecal metagenomic profiles, we investigated the genomic consequences of microbial exposure in the host. Colibactin-associated mutational signatures, SBS88 and ID18, were detected as early clonal events in a substantial fraction of Japanese CRCs and were particularly prevalent in younger patients. These mutational footprints provide a historical record of microbial genotoxic activity that cannot necessarily be captured by microbiome profiling at the time of diagnosis.

Together, these studies illustrate how moving beyond population-level associations toward strain-level characterization, functional validation, and host genomic footprints can provide deeper insight into microbial contributions to colorectal carcinogenesis. Such multi-layered resolution will be essential for distinguishing microbial biomarkers from microbial drivers and for ultimately developing microbiome-based strategies for cancer prevention and intervention.

FROM FOOD TO MICROBES: USING AI TO MAP THE DIET–GUT MICROBIOME CONNECTION

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Diet has emerged as the most relevant factor affecting the human gut microbiome. However, there is a lack of systematization of the overwhelming quantity of scientific literature addressing how different foods and diets affect the microbes present in the human gut. As a response, the Food & Microbes DB emerges as a tool to organize these food-microbe interactions in a functional standardized way that enables their systematic exploration. This AI-fed and human-curated database merges data leveraging thanks to AI models with human expertise and error correction. Not only were over 10,000 interactions between 1,024 foods and 1,265 microbes retrieved from 671 papers, but the database also presents information on the health group or population where the relation was observed, and the type of study and experimental methods applied to document these relations. The Food & Microbes DB user interface offers different search options with the aim of showing the most precise information possible. Searches can be conducted based on concrete foods, taxa and health groups or populations, as well as combinations of these, in order to find specific relations. In all, Food & Microbes DB is the first knowledge base designed for the systematic exploration of the effects of different foods, diets and nutrients on microbial abundances in the gut microbiome. Its use should provide an easy, structured and functional way to retrieve accurate, relevant and updated information relating to food and the microbiome. Therefore, Food & Microbes DB will contribute to enable an evidence-based path towards personalized dietary recommendations capable of modifying an individual's gut microbiome towards a health-promoting state.

GROWTH AND BODY COMPOSITION IN GNOTOBIOTIC MICE RECEIVING MICROBIOTA FROM INFANTS CONSUMING A MEAT- VS. DAIRY-BASED COMPLEMENTARY DIET

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Objectives: To determine the role of gut microbiota in infant growth.

Methods: We previously demonstrated that U.S. infants consuming a meat-based complementary diet had greater linear growth with same weight gain, compared to a dairy-based complementary diet, from 5 to 12 months. Infant stool samples at 12 months were transplanted into 4-week-old germ-free mice. Mice consumed a standard chow diet from 4 to 8 weeks.

Results: Significant differences in microbial composition between the meat and dairy group mice at week 8. Food intake or body weight did not differ between groups or by sex. MRI scans showed that female mice of the dairy group had greater abdominal fat ($11.4 \pm 3.4\%$ vs. $9.3 \pm 1.7\%$, $P=0.06$) and total body fat (1974 ± 508 vs 1658 ± 331 mm³, $P=0.06$) than female mice of the meat group at week 8. CT scans found that female mice from the meat group had greater tibia length gains than female mice from the dairy group (1.62 ± 1.04 vs. 0.95 ± 1.05 , $P=0.088$). Male mice did not show differences in body composition or bone length between groups.

Conclusions: Findings in female gnotobiotic mice were consistent with their microbiota donors. Future research needs to investigate the potential sex differences in the growth phenotypes.

Supported by National Institutes of Health (NIH)

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LONG-READ METAGENOMICS RESOLVES THE GUT MICROBIOTA OF A LONG-LIVED DOMESTIC CAT

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Introduction: Gut microbiota composition has been linked to longevity in human centenarian studies, but comparable genome-resolved data are lacking for companion animals. We specially selected a 21-year-old domestic cat, well beyond the typical feline lifespan of 12-18 years, to ask how completely a single long-read fecal metagenome resolves the gut microbiota of such an exceptional individual.

Material & Methods: Intact DNA was extracted from a single fecal sample by enzymatic digestion and sequenced using long-read (HiFi) technology. Reads were assembled and binned with SemiBin2 [1]. Bin quality was assessed with CheckM2 [2], and taxonomy assigned with GTDB-Tk [3] against GTDB R232. Redundancy among the 86 bins was resolved by average nucleotide identity.

Results: This resolved 69 non-redundant genomes from a single individual, including 16 complete, closed circular bacterial chromosomes ranging from 1.76 to 3.33 Mb, with completeness exceeding 97% (median 99.7%) and contamination below 3%.

Conclusion: Long-read metagenomics can thus resolve a near-complete, high-quality genome catalogue from a single exceptional individual, providing a foundation for exploring gut microbiota features associated with feline longevity.

Supported by COI-NEXT

ADAPTIVE EVOLUTION OF STAPHYLOCOCCUS AUREUS PROMOTES BACTERIAL SURVIVAL AND FUNCTIONAL MODULATION OF PERITONEAL MACROPHAGES DURING INFECTION

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Introduction: Staphylococcus aureus is a major cause of hospital outbreaks. The accessory gene regulator (Agr) supports bacterial adaptation, while peritoneal macrophages may provide a niche for persistence. We previously isolated environmentally adaptive (EA) S. aureus strains from a neonatal intensive care unit (NICU). Here, we investigated their effects on peritoneal macrophage responses.

Material & Methods: Isolates from 35 NICU patients were assessed for Agr activity and relatedness by core-genome phylogeny. Closely related Agr-positive, agr-mutant, and EA-agr clones were selected. Mice were infected for 1, 3, or 7 days and peritoneal lavage was analysed for bacterial burden and cytokines. Parallel infections and inhibitor studies were performed in vitro.

Results: Under low aeration, EA-agr strains reversibly silenced Agr despite high population density, phenocopying agr mutants. Agr-positive and EA-agr strains showed greater colonisation than agr mutants in vivo and in vitro. Agr-positive infection reduced mouse survival and increased IL-6, whereas EA-agr induced IL-10. An undisclosed AgrA inhibitor and antibacterial coumarin derivative 4 both significantly reduced intracellular bacterial burden in macrophages in vitro.

Conclusion: Reduced DNA methylation contributes to reversible Agr silencing, promoting immune evasion, macrophage persistence, and prolonged colonisation. The activity of two AgrA inhibitors identifies AgrA as a pharmacologically tractable target for persistent infection.

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Second Conjoint Meeting of RIKEN-ISM

Tokyo Targeting Microbiota

Abstracts of Day 2

September 25, 2026



THE MICROBIOTA SENDS THE SIGNAL. DO MITOCHONDRIA DECIDE THE RESPONSE?

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The gut microbiota continuously signals to host cells through metabolites, bacterial vesicles and diet-derived molecules. However, the biological effect of these signals may also depend on the capacity of host cells to respond.

Mitochondria could play a central role in this dialogue. Beyond energy production, they regulate metabolic flexibility, redox balance, inflammation and cellular adaptation. With ageing, chronic inflammation or metabolic disease, mitochondrial dysfunction may alter the cellular response to otherwise beneficial microbial signals.

Recent studies illustrate this interaction: microbiota-derived metabolites can modulate mitochondrial respiration and inflammatory responses, while bacterial extracellular vesicles can influence mitochondrial function and cell survival.

We propose a simple concept: the microbiota sends the signal, while mitochondria help shape the response. Understanding both sides of this dialogue may open new strategies combining microbiota modulation with preservation or restoration of mitochondrial competence.

THE MITOCHONDRIA–MICROBIOTA DIALOGUE: IMPACT ON HEALTH

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Mitochondria are central organelles that determine cellular responses to metabolic, oxidative, and inflammatory stresses. In the context of the microbiota–mitochondria axis, microbiota-derived metabolites and inflammatory cues are increasingly recognized as important extrinsic factors that influence mitochondrial function and cellular resilience.

Therefore, technologies that can deliver bioactive molecules directly to mitochondria provide a powerful strategy to modulate mitochondrial function and enhance cellular stress tolerance. Our laboratory has developed mitochondria-targeted nanocapsules, including the MITO-Porter, a lipid-based nano capsule designed to deliver cargoes to mitochondria via membrane fusion with mitochondrial membranes. This platform allows mitochondrial delivery of a wide range of molecules that are difficult to introduce by conventional targeting strategies, including small molecules, antioxidants, nucleic acids, and higher-order molecular assemblies. In this lecture, I will summarize our efforts to engineer mitochondrial function using mitochondria-targeted drug delivery systems. First, I will introduce the concept of MITO-Porter and its membrane-fusion-based delivery mechanism. I will then discuss applications in the regulation of mitochondrial oxidative stress, mitochondrial RNA/nucleic acid delivery for controlling mitochondrial gene expression, and the generation of mitochondria-activated therapeutic cells, termed MITO Cells. I will also introduce our recent e-MITO concept as an emerging strategy for controlling mitochondria-related cellular phenotypes. Finally, I will discuss how mitochondrial nanomedicine may contribute to cellular resilience, stress tolerance, and future therapeutic strategies for aging-associated mitochondrial dysfunction, with particular emphasis on how mitochondrial-side interventions may complement studies of microbiota-driven regulation of host physiology.

CAROTENOID METABOLISM REGULATES THE MICROBIOTA–MITOCHONDRIA AXIS: FROM DIET TO SINGLE-CELL HETEROGENEITY

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Dr. Dingbo Lin, the John and Sue Taylor Professor of Nutrition at Oklahoma State University, will present new evidence on how carotenoid metabolism shapes communication between the gut microbiome and mitochondrial function, with important implications for metabolic health and disease prevention.

Using mouse models with disrupted carotenoid metabolism via β -carotene oxygenase 2 (BCO2) knockout, Dr. Lin's team has shown that astaxanthin supplementation significantly remodels gut microbiota composition, enriching beneficial species such as *Akkermansia muciniphila*, while reducing key inflammatory markers, including NLRP3 inflammasome activation. These microbial shifts are accompanied by mitochondrial remodeling, including altered respiratory supercomplex assembly and redox balance.

This presentation highlights the microbiota – mitochondria axis as a critical interface between nutrition and metabolic resilience, offering fresh perspectives on how dietary bioactives may be harnessed to prevent obesity, diabetes, and immune-related conditions.

LIVING PROBIOTICS, MICROBIAL METABOLITES, AND MITOCHONDRIAL RESILIENCE: A PATHWAY TO HEALTHY AGING

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Prof. Dongryeol Ryu leads the Molecular and Integrative Biology (MIB) Lab at GIST, will discuss how microbiota-derived metabolites directly enhance mitochondrial resilience and promote healthy aging, positioning the gut microbiome as a source of bioactive compounds that sustain mitochondrial quality control and delay age-associated

functional decline.

Mitochondrial decline is a hallmark of aging, driving sarcopenia, metabolic dysfunction, and systemic frailty. Prof. Ryu's work sits at the convergence of microbiome science and mitochondrial biology, demonstrating that specific microbial metabolites can activate endogenous protective pathways to counteract this decline.

During his talk, he will present a two-part framework. First, he will summarize recent advances in Urolithin A (UA), a microbiota-derived metabolite that has emerged as a leading example of translational microbiome therapeutics for aging and muscle health. Second, he will introduce his group's recent work on 3-phenyllactic acid (PLA), a metabolite produced by *Lactiplantibacillus plantarum*, which shows translational relevance in patients with sarcopenia. Finally, he will share ongoing efforts to identify next-generation microbiota-derived metabolites that may further expand the therapeutic landscape for healthy aging and systemic resilience.

BIDIRECTIONAL INTERACTIONS BETWEEN GUT MICROBIOTA AND HOST ENERGY METABOLISM DURING Q-NEURON-INDUCED TORPOR

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Introduction: Activation of quiescence-inducing neurons (Q neurons) induces a multi-day torpor-like state with body temperature of approximately 25°C and oxygen consumption at one-quarter of baseline, termed the Q-neuron-induced hypothermic/hypometabolic state (QIH)¹. In this study, we investigated gut microbiota dynamics during QIH and examined their contribution to host metabolic response.

Material & Methods: The gut microbiota of mice was analyzed throughout QIH by shotgun metagenomic sequencing. To identify factors driving microbial changes during QIH, the gut microbiota was also analyzed in fasted or anesthesia-induced hypothermic mice. Additionally, gut microbes were depleted with an antibiotic cocktail to assess their role in QIH, and basal metabolism and recovery from QIH were evaluated.

Results: QIH caused transient changes in gut microbial composition, with decreased *Lactobacillus* spp. and expansion of *Escherichia coli* in the small intestine. *E. coli* expansion occurred during anesthesia-induced hypothermia but not fasting, suggesting that hypothermia drives this shift. Notably, antibiotic treatment further reduced body temperature and oxygen consumption during QIH and markedly delayed recovery.

Conclusion: QIH alters the gut microbiota, including hypothermia-driven *E. coli* expansion. Conversely, microbiota depletion further lowered basal metabolism during QIH, suggesting a role for gut microbiota in host metabolic adaptation. Further studies are needed to clarify their physiological significance.

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STRAIN- AND FUNCTION-RESOLVED METAGENOMICS TO IDENTIFY MICROBIAL DRIVERS OF CHRONIC DISEASE

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The human gut microbiome is highly diverse, with important biological differences occurring not only between species but also between individual microbial strains. Conventional taxonomic profiling may therefore overlook functions directly relevant to disease.

Strain- and function-resolved metagenomics provides a higher-resolution view of the microbiome, enabling the identification of microbial genes, pathways and strain-specific features associated with host phenotypes and chronic diseases.

This approach can help move microbiome research from association toward mechanism, identifying microbial functions that may serve as biomarkers or potential targets for prevention and precision intervention.

PRECISION MICROBIOME THERAPEUTICS TO ENHANCE CANCER IMMUNOTHERAPY

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Dr. Sin-Hyeog Im, a leading expert in immunology and microbiome research, will discuss how precision microbiome therapeutics can reshape cancer immunotherapy by harnessing the complex interactions between gut microbiota and the host immune system.

Our immune system maintains homeostasis through a delicate balance between active immunity and tolerance, governed by the coordinated interaction of genetic factors and environmental cues, including intestinal microbiota. Dysregulation of commensal flora is closely linked to immune disorders, neurological conditions, and metabolic syndromes, and it significantly influences varied responses to immune checkpoint inhibitors targeting PD-L1/PD-1 and CTLA-4. Candidates for microbiome therapy include bioactive metabolites, cellular components, and live biotherapeutic products (LBPs).

During his talk, Sin-Hyeog Im will present Avatiome™, an innovative platform screening system that mimics the human body's immune system and microbiome, integrating immunophenotyping, single-cell transcriptomics, and artificial intelligence to identify immunostimulatory microorganisms. He will discuss the discovery of IMB001, a candidate with anti-cancer activity, and the underlying mechanisms of its effector molecules across diverse pre-clinical models, as well as their potential therapeutic applications.

This presentation, positioned at the intersection of biotechnology innovation and microbiota-based therapies, aligns with Session 4: Therapeutic Interventions for Healthy Aging. It links precision probiotics, metabolite therapeutics, microbiota-driven metabolic interventions, and startup-led biotech innovation to highlight practical approaches for enhancing systemic health and resilience.

DEVELOPMENT OF SMART BIODELIVERY SYSTEMS FOR PERSONALIZED DISEASE TREATMENT BASED ON THE GUT MICROBIOME

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Dr. GwangPyo Ko, Professor of Environmental Health Microbiology at Seoul National University, will present a creative new approach to treating intestinal inflammation: engineering the gut's own bacteria to deliver therapeutics precisely where disease strikes.

During colitis, the gut microbiota undergoes dramatic shifts. Rather than viewing these changes as purely harmful, Dr. Ko's team identified an opportunity: *Phocaeicola vulgatus*, a commensal bacterium that naturally expands in inflamed gut tissue in both humans and mice while remaining nonpathogenic. By engineering this inflammation-enriched resident to secrete anti-inflammatory proteins directly at disease sites, his team has created a living drug delivery system that works with the body's own microbial ecology rather than against it.

This presentation offers a glimpse into the future of microbiome medicine: ecologically grounded, precision-targeted living therapeutics that harness the gut's own adaptive biology to treat chronic inflammatory disease.

GUT COMMENSALS ALLEVIATE ATHEROSCLEROSIS BY MODULATING CHOLESTEROL METABOLISM

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The gut microbiota plays a pivotal role in human health, yet the molecular mechanisms through which gut microbes influence host physiology remain poorly understood. *Bacteroides*, a dominant genus of the human gut microbiota, is depleted in patients with atherosclerosis, but causal evidence linking these bacteria to disease progression remains limited. Here, we show that administration of a gut *Bacteroides* strain alleviates atherosclerosis in mice and improves host cholesterol homeostasis. Through bioactivity-guided screening, we identified a microbiota-derived small molecule that mediates this protective effect. Mechanistic studies revealed that this metabolite directly targets a key enzyme in hepatic cholesterol metabolism, leading to reduced cholesterol biosynthesis, enhanced low-density lipoprotein receptor (LDLR) expression, and increased plasma LDL-cholesterol clearance. Comparative chemical analyses further identified the major microbial producers of this metabolite in the human gut. Importantly, circulating levels of the metabolite were markedly reduced in individuals with dyslipidemia, supporting its potential relevance to human cholesterol homeostasis. Together, these findings uncover a previously unrecognized chemical mechanism underlying gut microbiota–host metabolic communication and provide a potential framework for microbiome-based intervention in cardiovascular disease.

CD19 CAR T CELL THERAPY RESHAPES THE HOST MICROBIOTA IMMUNE AXIS IN AUTOIMMUNE DISEASES

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Introduction: CD19-targeted CAR T-cell therapy induces profound B-cell depletion and clinical responses in autoimmune disease(ref1-3), but how it resets B-cell immunity and reshapes host-microbiota interactions remains unknown.

Material & Methods: We longitudinally profiled gut microbiota composition and mucosal humoral immunity in autoimmune disease patients undergoing CD19-targeted CAR T-cell therapy using shotgun metagenomics, IgA/IgG-bound microbiota profiling, and PhIP-seq-based antibody repertoire analysis.

Results: CAR T-cell therapy profoundly remodeled microbiota-directed humoral immunity, inducing coordinated remodeling of microbial composition, IgA/IgG-coated bacterial communities, and microbiota-reactive antibody repertoires, while preserving pathogen-experienced antibody responses. Integrated host-microbiome analyses revealed alterations in predicted microbiota-host interaction networks affecting B-cell-microbiota protein interactions, in particular with the immunoproteasome that associated with the risk of relapse. Baseline mucosal immune signatures, including fecal IgA levels, were associated with subsequent B-cell reconstitution. Tracking immunologically active taxa longitudinally revealed significant depletions of Bifidobacterium adolescentis after CAR T-cell therapy.

Conclusion: These findings demonstrate profound remodeling of the host-microbiota immune axis after CAR T-cell therapy and identify the intestinal immune compartment as a potentially modifiable determinant of immune recovery.

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CROSS-SITE ORAL AND ESOPHAGEAL MICROBIOME SIGNATURES DEFINE DIAGNOSTIC PATTERNS AND REVEAL MECHANISTIC DRIVERS OF ESOPHAGEAL SQUAMOUS CELL CARCINOMA

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Introduction: Oral cavity and esophagus are contiguous mucosal sites whose microbiomes may jointly influence esophageal squamous cell carcinoma (ESCC). However, whether microbial alterations are shared across oral and esophageal niches and possess diagnostic potential for ESCC remain largely unknown.

Materials & Methods: Paired oral swabs and esophageal tumor biopsies from 45 ESCC patients and matched controls underwent high-depth five-region 16S rRNA sequencing. Microbial diversity, taxonomic composition, differential taxa, and diagnostic performance were analyzed using standard bioinformatics approaches. PICRUST2 predicted microbial functional alterations, and a 4-NQO/*Porphyromonas gingivalis*-induced ESCC mouse model was used to investigate the associated immune mechanisms.

Results: We identified consistent enrichment of *Fusobacterium*, *Porphyromonas*, and *Treponema*, with concurrent depletion of *Neisseria*, *Rothia*, and *Actinomyces* across both oral and esophageal niches. These cross-site microbial signatures showed excellent diagnostic performance (AUC>0.9), supporting proof-of-concept for non-invasive ESCC detection using oral swab microbiome profiles. Functional prediction revealed enrichment of nucleotide, amino sugar, and glycan metabolism, with reduced fatty acid metabolism. In the mouse model, *P. gingivalis* accelerated ESCC development, increased pro-inflammatory cytokine production, DC-PD-L1 expression, and STAT3 activation.

Conclusion: These findings support a microbiome-mediated pro-tumorigenic niche and the development of an oral microbiome-based diagnostic code for ESCC, pending validation in larger independent cohorts.

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RAMAN-ACTIVATED CELL SORTING: A NOVEL PLATFORM FOR LABEL-FREE, NON-DISRUPTIVE SINGLE-CELL METABOLIC PHENOTYPING

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Label-free, noninvasive, rapid and cost-efficient: combining Raman spectroscopy with high-throughput flow cytometry reveals the metabolic performance of individual cells of a population in their natural context.

Understanding metabolic heterogeneity at the single-cell level is essential for characterizing cellular function. eCyte's Raman-activated cell sorting platforms combine single-cell Raman spectroscopy with precision sorting to identify and isolate living cells based on their biochemical fingerprints, without fluorescent labels or staining. Designed to minimize disruption to cell viability and integrity, these platforms enable metabolic phenotyping and recovery of selected cells for downstream cultivation or sequencing. This approach connects functional phenotypes with molecular analysis, opening opportunities for microbial screening, biotechnology, and investigation of complex cellular populations.

NEW-GENERATION POMEGRANATE METABOLITES & THE GUT–MUSCLE AXIS: A MICROBIOME STRATEGY FOR MUSCLE PRESERVATION DURING GLP-1 THERAPY

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Introduction: GLP-1 therapy produces substantial weight loss but may also reduce lean tissue, creating a need for interventions that preserve muscle quality and function. Naturally fermented pomegranate provides natural urolithins within a full-spectrum matrix of pomegranate metabolites capable of influencing the gut–muscle axis. The present study evaluated whether this metabolite network could preserve lean mass by coordinating microbiome remodeling, short-chain fatty-acid production, mitochondrial substrate handling, mitophagy, mitochondrial biogenesis, and inflammatory regulation during GLP-1 therapy.

Material & Methods: A 16-week, randomized, double-blind, placebo-controlled, parallel-group trial enrolled 60 adults aged 40–70 years with BMI 27–40 kg/m² receiving stable maintenance-dose semaglutide (1.7 or 2.4 mg weekly). Participants were randomized 1:1 to Test product (500 mg/day) or matched placebo. Both groups received identical protein and resistance-exercise guidance. The primary endpoint was change in DXA appendicular lean mass (ALM); total lean and fat mass were measured at Weeks 0 and 16. Handgrip strength and 6-minute walk distance were assessed at Weeks 0, 8 and 16. Plasma urolithins, acylcarnitines, circulating biomarkers, stool short-chain fatty acids (SCFA) and eight targeted bacterial taxa were evaluated at Weeks 0 and 16. PINK1, PARKIN, LC3-II/LC3-I and PGC-1 α were measured in a PBMC subgroup (15/group).

Results: Despite comparable weight loss, ALM was maintained with Test product (–0.1%) but declined with placebo (–2.9%; adjusted difference +0.74 kg, 95% CI 0.37–1.11, $p < 0.001$). Total lean-mass difference was +0.81 kg ($p < 0.01$); lean tissue comprised 7.0% versus 25.5% of weight lost ($p < 0.01$). Handgrip strength and 6-minute walk distance trended favourably but non-significantly. Fasting urolithin A detection rose from 37% to 80% with Test product, versus 34% unchanged with placebo (between-group $p < 0.001$). Medium- and long-chain acylcarnitines were 12% and 14% lower; butyrate, propionate and total SCFA 25%, 14% and 6% higher; GDF-15 and hs-CRP 12% and 21% lower (all $q < 0.01$). Akkermansia muciniphila, Faecalibacterium prausnitzii and Anaerobutyricum soehngenii increased; Ruminococcus gnavus, Bilophila wadsworthia, Desulfovibrio piger and Enterobacteriaceae decreased (all $q < 0.001$). PBMC PINK1, PARKIN, LC3-II/LC3-I and PGC-1 α increased (all $q < 0.05$).

Conclusion: Natural urolithins and full-spectrum pomegranate metabolites produced an integrated gut–muscle response extending beyond any single constituent. Concurrent modulation of microbial ecology, SCFA production, inflammatory signaling, acylcarnitine metabolism, PINK1–PARKIN mitophagy, and PGC-1 α -associated mitochondrial biogenesis provides mechanistic support for preservation of muscle mass and function during GLP-1 therapy.

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FROM DISCOVERY TO IMPLEMENTATION OF NATURAL PRODUCT-DERIVED POSTBIOTIC METABOLITES

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One of the major challenges in natural product research is the identification of active principles responsible for the therapeutic effects of traditionally used medicinal plants. Attempts to explain their activity solely through the original chemical composition of plant material often lead to incomplete conclusions. However, such apparent failures can become valuable turning points, redirecting attention from the administered natural products to the molecules generated from them within the host organism.

The gut microbiota represents a metabolically active ecosystem that has co-evolved with humans and has been continuously exposed to dietary constituents, xenobiotics, and specialized plant metabolites. As a result, commensal microorganisms have developed diverse biochemical strategies that influence host physiology, including digestion, immunity, nervous system function, nutrient metabolism, and xenobiotic transformation. In this context, the gut microbiota should be considered not only as a modifier of pharmacokinetics, but also as an active contributor to the formation of pharmacologically relevant molecules.

Studies conducted in the Microbiota Lab have demonstrated that natural products found in traditionally used plant materials can be transformed by human and animal gut microbiota into postbiotic metabolites with distinct chemical structures and biological properties. These findings outline a pathway from discovery to the potential implementation of postbiotic metabolites as pharmacologically active molecules. By embracing unexpected outcomes, this approach provides a new framework for understanding traditional medicines and supports the identification of lead compounds that may be further developed into active pharmaceutical ingredients.

A NOVEL MICROBIAL EXOPOLYSACCHARIDE FROM TULIP-DERIVED AUREOBASIDIUM PULLULANS FOR EPIDERMAL BARRIER-TARGETED PORE CARE

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Introduction: Native to high-altitude Central Asia, *Tulipa* thrives in dry, sun-drenched environments, harboring symbiotic microbes that produce protective compounds. Beyond conventional astringents, we investigated tulip-derived *Aureobasidium pullulans* HKtulip002 to pioneer structural pore refinement via epidermal barrier gene regulation using exopolysaccharides (EPS).

Material & Methods: EPS yield was maximized via fermentation media optimization and solvent precipitation. Polysaccharides were profiled via UV-Vis. Bioactivity and barrier pathways were evaluated using qRT-PCR and Oil Red O staining. A 2-week clinical trial assessed pore refinement (IRB: 2024-12-006).

Results: Bioprocess optimization achieved a 5-fold yield increase (75.93% pullulan, 14.83% glycosaminoglycans). Clinically, 1% EPS refined pores, reducing count by 11.06% and area by 18.90%. These effects were attributed to enhanced barrier function, reduced transepidermal water loss (TEWL), and regulated sebum balance. Mechanistically, 100 µg/mL EPS suppressed lipogenesis and upregulated barrier genes, filaggrin (FLG) by 182.32% and claudin-1 (CLDN1) by 52.35%.

Conclusion: This study proves microbial EPS achieves structural pore refinement by transcriptionally strengthening the epidermal barrier rather than merely suppressing surface sebum.

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LONGITUDINAL GUT MICROBIOME MODULATION BY A POLYHERBAL FORMULATION DURING METFORMIN THERAPY A RANDOMIZED CROSSOVER TRIAL

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Introduction: Metformin is a first-line type 2 diabetes therapy, but gastrointestinal intolerance may limit its use[1]. We previously observed rapid gut microbiome changes following addition of a polyherbal formulation (PHF) to metformin[2]. Here, we investigated the longitudinal dynamics of these effects in a completed 48-week randomized crossover trial (NCT06846138).

Material & Methods: Fifty-one adults with T2D (70.6% women; age: 62.3±10.7 years; median BMI: 34.9 kg/m²) participated in a 48-week randomized, placebo-controlled crossover intervention. Participants received a PHF or placebo as add-on to metformin and switched interventions after 24 weeks. Longitudinal stool samples were analysed by shotgun metagenomics. Treatment-by-time effects were assessed using linear mixed-effects models accounting for treatment sequence, age, sex and repeated measurements. Stool metabolomics is ongoing.

Results: We identified 62 significant species-level treatment-by-time associations (FDR<0.05), including 53 at day 7 and nine at month 6. Early effects confirmed enrichment of Bifidobacterium, including *B. ruminantium* ($\beta=2.59$; FDR=1.06×10⁻⁴) and *B. angulatum* ($\beta=1.91$; FDR=3.5×10⁻⁵), while later associations involved a distinct subset of taxa. Functional profiling identified 12 significant pathway interactions at day 7, including increased Bifidobacterium shunt activity ($\beta=2.84$; FDR=1.35×10⁻⁴).

Conclusion: PHF induces time-dependent taxonomic and functional microbiome modulation during metformin therapy, characterized by a strong early Bifidobacterium-associated response and distinct longer-term microbial effects.

Supported by: Latvian Council of Science (Fundamental and Applied Research Project No. Izp-2023/1-0422 'MetHerb: Enhancing the efficacy and tolerability of metformin in the analysis of gut microbiome by add-on polyherbal formulation').

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EARLY-LIFE SUPPLEMENTATION WITH BIFIDOBACTERIUM LONGUM SUBSP. INFANTIS YLGB-1496 SUPPORTS GASTROINTESTINAL MATURATION IN HEALTHY FORMULA-FED INFANTS: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Our multicenter, randomized, double-blind, placebo-controlled trial evaluated whether supplementation with *Bifidobacterium longum* subsp. *infantis* YLGB-1496 (*B. infantis*) promotes gastrointestinal maturation in healthy infants. Healthy term infants aged 0–6 months who were formula-fed or mixed-fed received *B. infantis* or placebo for 12 weeks, while an exclusively breastfed group served as a physiological reference. Defecation frequency, stool characteristics, and defecation-related behaviors were assessed longitudinally, and gut microbiota composition was analyzed using full-length 16S rRNA gene sequencing. Longitudinal mixed-effects models and correlation analyses examined associations between microbial taxa and gastrointestinal outcomes. A total of 145 infants with post-baseline data were included. Compared with placebo, *B. infantis* improved defecation-related behaviors and shifted gastrointestinal outcomes toward those observed in breastfed infants. Fecal α 1-antitrypsin showed a significant group-by-time interaction ($P = 0.008$). Supplementation increased the relative abundance of Actinobacteriota and selectively enriched *Bifidobacterium longum*, *Pediococcus acidilactici*, and *Lactocaseibacillus rhamnosus*, without significant changes in α - or β -diversity. *B. longum* was consistently the taxon most strongly associated with favorable defecation outcomes.

These findings suggest that targeted enrichment of infant-associated bifidobacteria may support early gastrointestinal maturation and intestinal barrier development.

Second Conjoint Meeting of RIKEN-ISM Tokyo Targeting Microbiota

Abstracts of Poster Presentations

Alphabetical Order



THE INTERPLAY BETWEEN GUT MICROBIOTA, INFLAMMATION, AND NEURODEVELOPMENTAL DISORDERS: A FOCUS ON AUTISM SPECTRUM DISORDER

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Introduction: Autistic individuals often experience inflammatory disorders and gastrointestinal issues, possibly related to gut microbiome changes¹. We studied how acute inflammatory insult (Dextran-sulfate-sodium; DSS treatment) affects the gut microbiome in Nlgn3R451C mice with an autism-associated Neuroligin-3 variant² and IFNAR1^{-/-} mice lacking the immune response receptors interferon alpha/beta subunit-1.

Methods: Ulcerative colitis symptoms were generated in 8-week-old Nlgn3R451C, IFNAR1^{-/-}, Nlgn3R451CxIFNAR1^{-/-} and wild-type mice with 3%-DSS for 7 days. Faecal samples were collected during DSS treatment, and 16S rRNA gene sequencing was used to profile the gut microbiota.

Results: DSS treatment negatively impacted microbial alpha-diversity in wild-type mice (P=0.017), particularly on Day 8 versus SHAM-treated mice (P=0.03). Microbial diversity also changed in DSS-treated Nlgn3R451CxIFNAR1^{-/-} mice (P=0.013) and IFNAR1^{-/-} mice (P=0.02). In contrast, DSS-treated Nlgn3R451C mice showed no diversity changes across time. Lachnospiraceae_Nk4A136_group dominated in all mouse models. Romboutsia and Akkermansia increased with DSS, especially on Day 8. Akkermansia was abundant in Nlgn3R451C and IFNAR1^{-/-} mice.

Conclusions: Unlike wild-type mice, Nlgn3R451C mice showed unchanged gut microbial alpha diversity after DSS treatment. Akkermansia levels increased with DSS treatment in Nlgn3R451C mice, suggesting opportunistic and potentially protective growth of Akkermansia in response to DSS-induced colitis. This autism-associated variant impacts gut microbiota in response to inflammation.

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PLASMA TMAO LEVELS ARE ASSOCIATED WITH VASCULAR CALCIFICATION IN TAKAYASU ARTERITIS

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Background: Trimethylamine-N-oxide (TMAO), a gut microbiota-dependent metabolite of dietary choline, phosphatidylcholine and L-carnitine, has been linked to vascular calcification, chronic kidney disease and vascular disease progression (1-3). Its role in Takayasu arteritis (TAK) is unknown. We assessed the association between plasma TMAO and CT-quantified aortic calcification in TAK.

Methods: We retrospectively studied 62 patients with TAK and 62 age- and sex-matched healthy volunteers. Plasma choline and TMAO were measured by LC-MS. Whole-body arterial calcification was quantified by Agatston score, with follow-up CT in TAK.

Results: Choline levels were similar between groups (755 [675–840] vs 778 [686–960] ng/mL, $p=NS$), whereas TMAO was higher in TAK (197 [124–394] vs 124 [86–243] ng/mL, $p=0.024$). In TAK, TMAO correlated with Agatston score ($r=0.273$, $p=0.032$). Patients above the median TMAO (200 ng/mL; $n=31$) had lower eGFR (63 ± 21 vs 78 ± 14 , $p=0.017$), higher Agatston scores (4095 [995–18206] vs 1171 [98–9467], $p=0.041$), and more TAK-related vascular lesions (70% vs 32%, $p=0.002$). Over 12 months, Agatston score progression was greater in the higher-TMAO group (25% [15–92] vs 2% [0–9], $p=0.024$).

Conclusions: Elevated TMAO is associated with vascular calcification and its progression in TAK, and may serve as a novel biomarker for vascular events.

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HELICOBACTER ASSOCIATED MICROBIAL SIGNATURES IN GASTRIC CANCER: INSIGHTS FROM NANOPORE FULL-LENGTH 16S RRNA SEQUENCING IN CHILEAN POPULATIONS

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Gastric cancer progression is accompanied by dynamic restructuring of the gastric microbiome, including shifts associated with declining of *Helicobacter* abundance and the emergence of non-*Helicobacter* taxa. Gastric tissues from 83 Chilean individuals from two independent cohorts were analyzed using full-length 16S rRNA nanopore sequencing: the MAGIC Magallanes cohort from Punta Arenas, in sub-Antarctic Chile, and the Biobank of Tissues and Fluids from the University of Chile cohort from Santiago, Chile. Samples were stratified according to *Helicobacter* relative abundance, and microbial diversity, taxonomic composition, and predicted metabolic pathways were evaluated across disease stages. In superficial gastritis and intestinal metaplasia, *Helicobacter*-negative samples exhibited significantly higher microbial diversity and distinct bacterial community structures compared with *Helicobacter*-positive samples. Decreased *Helicobacter* was associated with enrichment of several non-*Helicobacter* genera. In superficial gastritis, *Cutibacterium* and *Pseudomonas* showed strong negative correlations with *Helicobacter*, whereas in intestinal metaplasia, *Actinomyces*, *Streptococcus*, *Veillonella*, *Alloscardovia*, and *Fusobacterium* increased as *Helicobacter* declined. Functional pathway analysis revealed that reduced *Helicobacter* abundance was associated with pathways related to degradation and utilization processes, biosynthesis, and central energy metabolism.

These **findings** suggest that declining *Helicobacter* during gastric carcinogenesis is accompanied by expansion of non-*Helicobacter* microbial communities and metabolic restructuring that may contribute to disease-associated microbial signatures.

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DISEASE SPECIFIC GUT MICROBIAL SIGNATURES GENERATE MODEL DERIVED CANCER PROBABILITY SCORES THROUGH TARGETED FECAL QPCR PROFILING

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The gut microbiome is a potential source of non-invasive cancer biomarkers. We evaluated six fecal microbial markers and developed targeted qPCR-based logistic models for colorectal cancer (CRC) and pancreatic cancer (PC). Using LASSO with the 1-standard-error rule, four markers were selected for CRC (afb, nan, fsr, and 5ar) and three for PC (but, fsr, and saa). In post-selection leave-one-out cross-validation of fixed model structures, the CRC and PC models yielded AUCs of 0.824 and 0.780, respectively. Fixed-model application yielded AUCs of 0.716 for colorectal adenoma and 0.540 for the pancreatic high-risk group. In an exploratory Early PC versus high-risk comparison, the fecal qPCR score showed a higher AUC point estimate than CA19-9, while the difference was not statistically significant. Overall, the disease-specific model performance and fixed-model behavior across clinically related groups support further evaluation of model-derived cancer probability scores as exploratory cancer-assessment tools.

Key findings reproduced from the 2026 BBB paper and integrated with additional exploratory data.

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ROLE OF ADVANCED GLYCATION END PRODUCTS AND THEIR RECEPTORS IN THE ASSOCIATION BETWEEN EXPOSURE TO METAL FUME PARTICLES AND INTESTINAL PERMEABILITY

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Introduction: Welders generate metal fume particles that enter the body via inhalation or ingestion, increasing advanced glycation end-product (AGE) production and posing risks to the intestinal barrier and gut microbiota. Human studies on AGEs, gut microbiota, and intestinal permeability remain limited. This study examines associations between metal fume exposure, AGEs, gut microbiota, and intestinal permeability.

Material & Methods: We recruited 57 participants in a longitudinal study at a shipyard in northern Taiwan (2022–2023). Air sampling preceded blood and stool collection. Heavy metals were detected by ICP-MS. Zonulin, calprotectin, AGEs, and sRAGE were detected by ELISA, and skin AGE accumulation by autofluorescence (SAF). Gut microbiota was analyzed by 16S rDNA sequencing.

Results: Fecal iron and manganese categorized high and low internal dose groups; serum AGEs were significantly higher in the high-dose group. GEE analysis showed AGEs positively associated with fecal copper. Calprotectin was negatively associated with vanadium, chromium, arsenic, and lead, while zonulin was positively associated with lead. Fecal metals were significantly associated with gut bacteria, and both *Lachnoclostridium* and sRAGE mediated the lead–zonulin association.

Conclusion: Significant associations existed between fecal metals, plasma AGEs, intestinal permeability biomarkers, and gut bacteria richness, along with mediation effects among metals, AGEs, and gut microbiota.

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GUT MICROBIOME REMODELING IS ASSOCIATED WITH IMPAIRED SECONDARY ARSENIC METHYLATION IN ADULTS CHRONICALLY EXPOSED TO GROUNDWATER ARSENIC

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Background: The gut microbiome may participate in arsenic biotransformation, but population evidence remains scarce. We examined how groundwater arsenic exposure reshapes microbial ecology and relates to host arsenic methylation.

Methods: Fecal shotgun metagenomes were analyzed from 258 adults in neighboring rural Chinese villages with contrasting groundwater arsenic concentrations (control, $n = 138$; exposed, $n = 120$). Urinary arsenic species were quantified in a subgroup ($n = 60$) to calculate primary and secondary methylation indices (PMI and SMI).

Results: Exposure was associated with altered microbial alpha diversity and community structure (PERMANOVA $P = 0.032$). Prevotellaceae and Prevotella-related genera were enriched in exposed participants, whereas Lachnospiraceae and Enterocloster were enriched in controls. Anaerovibrio slackiae, Eubacterium cellulosolvens, Coprococcus sp., and Clostridium spp. were positively associated with SMI after adjustment. Exposed microbiomes differed in ABC transporters, two-component systems, sulfur metabolism, xenobiotic degradation, and 13 arsenic metabolism-related genes, including MetK and multiple Ars-family genes. SMI, reflecting MMA-to-DMA conversion, was lower in exposed participants (FDR-adjusted $P = 0.019$), while PMI was unchanged.

Conclusions: Chronic arsenic exposure was associated with coordinated taxonomic and functional remodeling of the gut microbiome. Associations between fermentative taxa and secondary methylation suggest that microbial ecology may contribute to interindividual variation in arsenic detoxification.

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METAGENOMIC ANALYSIS REVEALS DONOR-ASSOCIATED ANTIBIOTIC RESISTANCE GENE DYNAMICS AFTER FECAL MICROBIOTA TRANSPLANTATION

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Fecal microbiota transplantation (FMT) can restore the gut microbiome, but its effects on antibiotic resistance genes (ARGs) remain underexplored. Because FMT transfers donor-derived microbial communities, it may introduce ARGs alongside beneficial functions.

To characterize post-FMT ARG dynamics, particularly the acquisition of donor-derived ARGs, we curated raw shotgun metagenomic data from six public FMT cohorts and processed them using a unified workflow. Samples were organized into FMT triads comprising one donor sample, one pre-FMT recipient sample, and at least one post-FMT recipient sample.

We compared ARG profiles across donor, pre-FMT, and post-FMT samples and quantified how these profiles changed after treatment. FMT reduced recipient ARG diversity and abundance, while donor-derived ARG signals remained detectable and post-FMT profiles shifted toward donor profiles. Several ARG families, including vancomycin- and tetracycline-associated genes, recurred across cohorts and were prominent in transfer-related analyses. We prioritized high-risk transferable ARGs based on occurrence and transfer frequencies across individual triads. Genus-level contribution analysis linked these ARG signals to a limited set of likely microbial contributors.

These results provide a multi-cohort framework for evaluating post-FMT ARG dynamics, identify transferable resistance features for downstream mechanistic investigation, and may help inform stricter donor-screening criteria to improve FMT safety.

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NASAL MICROTIOTA AS A MEDIATOR BETWEEN OCCUPATIONAL METAL FUME EXPOSURE AND RESPIRATORY HEALTH EFFECTS

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Introduction: Welding fume, a Group 1 IARC carcinogen, poses significant occupational respiratory risks. Nasal microbiota may mediate metal fume-induced respiratory effects, yet this role remains poorly understood.

Material & Methods: A two-year longitudinal repeated-measures study was conducted among 36 male shipyard workers in Taiwan (26 welders, 10 non-welders). Nasal microbiota was profiled by 16S rRNA gene sequencing; urinary metals by ICP-MS; EBC 8-isoprostane and IL-6 by ELISA. Analyses included GEE, qqcomp, and serial mediation analysis.

Results: Multiple urinary metals were positively associated with nasal *Corynebacterium*, which was consistently associated with improved lung function (FVC, FEV1, FEV1/FVC, MMF). qqcomp confirmed significant overall effects of 14-metal mixture on IL-6 and *Corynebacterium*. Serial mediation analysis showed *Corynebacterium* acted as a protective mediator, while *Staphylococcus* mediated a negative indirect effect of urinary nickel on FVC via IL-6.

Conclusion: Metal fume exposure induces nasal dysbiosis with divergent consequences. Mixture analysis corroborated single-metal findings, and mediation analysis revealed *Corynebacterium* confers respiratory protection while *Staphylococcus* exacerbates impairment via inflammation.

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ANTIBACTERIAL ACTIVITY OF THE CULTURE SUPERNATANT OF LACTIPLANTIBACILLUS PLANTARUM K9 AGAINST VARIOUS PATHOGENS ISOLATED FROM SWINE IN KOREA

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Lactiplantibacillus plantarum K9 holds strong potential for industrial application, as the strain has been validated for various functionalities, including the production of antimicrobial peptides (AMPs), antiviral activity, and lactic acid production. In this study, the antibacterial activity of the culture supernatant of *L. plantarum* K9 was evaluated against various pathogens isolated from swine in Korea. The culture supernatant of *L. plantarum* K9 was concentrated tenfold. *Clostridium perfringens*, F18+ *E. coli*, *Salmonella* Typhimurium, and *Streptococcus suis* strains were isolated from pigs. Three strains of each pathogen were tested. The minimum inhibitory concentrations (MICs) of the culture supernatant were determined using the microtiter plate method, following the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS). The supernatant was serially diluted twofold, ranging from 1:1 to 1:1,024. The MICs of the culture supernatant of *L. plantarum* K9 were 1:128 for *C. perfringens*, approximately 1:85 for F18+ *E. coli*, 1:64 for *S. Typhimurium*, and 1:256 for *Strep. suis*. These findings suggest that further research on the potential use of the culture supernatant of *L. plantarum* K9 as a feed additive to reduce diseases caused by these pathogens in pigs is warranted.

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GUT MICROBIOTA-DERIVED METABOLISM MAY CONTRIBUTE TO BLOOD PRESSURE REGULATION

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Introduction: Hypertension is affected by dietary salt intake and the gut microbiota (GM), yet the microbial functions involved in blood pressure regulation remain poorly understood. This study aimed to identify GM-derived metabolic pathways associated with blood pressure.

Material & Methods: Sixty individuals were selected from the Shika Study and classified into four groups according to mean blood pressure and urinary sodium excretion. Shotgun metagenomic sequencing was performed to compare gut microbial diversity and composition among the groups and to analyze microbial functional genes.

Results: Gut microbial diversity differed among the four groups. Individuals with normal blood pressure showed significantly higher abundances of genes encoding spermidine synthase, a key enzyme involved in polyamine biosynthesis, regardless of salt intake. Moreover, bacterial species harboring polyamine metabolism-related genes differed among the groups, suggesting differences in the functional profiles of the GM.

Conclusion: These findings suggest that GM-derived polyamine metabolism may contribute to blood pressure regulation and highlight the importance of functional metagenomic analysis for understanding the relationship between the gut microbiota and hypertension.

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α -CYCLODEXTRIN ATTENUATES BODY-WEIGHT GAIN AND MESENTERIC FAT ACCUMULATION IN FUSIMONAS INTESTINI-COLONIZED MICE

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Introduction: *Fusimonas intestini* (FI) produces elaidate, a trans-fatty acid that impairs intestinal barrier integrity and exacerbates high-fat-diet (HFD)-induced obesity. α -Cyclodextrin (α -CD) can form inclusion complexes with elaidate and may prevent its biological effects. In the present study, we examined the ability of α -CD to prevent elaidate-driven gut barrier dysfunction in the context of metabolic disorders.

Material & Methods: Germ-free mice colonized with TE17 (*Escherichia coli*) and FI (n=5/group) were fed HFD containing 0% or 10% α -CD. Body weight, food intake, adipose and liver weights, and serum lipid levels were assessed.

Results: α -CD significantly suppressed body-weight gain, while daily food intake and food intake relative to body weight did not differ between groups. Mesenteric fat mass relative to body weight was significantly lower in the 10% α -CD group, whereas peritesticular adipose and liver weights were unchanged. Serum triglycerides tended to be lower with 10% α -CD, although HDL, LDL, and total cholesterol did not differ significantly.

Conclusion: α -CD suppressed body-weight gain and mesenteric fat accumulation without reducing food intake, suggesting its potential as an intervention against elaidate-associated metabolic dysfunction.

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GUT-BRAIN AXIS FUNCTION IN EARLY NEURODEVELOPMENT: BEHAVIORAL CONSEQUENCES OF MICROBIOTA DEPLETION IN BETTA SPLENDENS

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Background: The gut-brain axis influences host behavior, but its role during early neurodevelopment in non-mammalian vertebrates is unclear. We used *Betta splendens* larvae, a teleost model enabling microbiota manipulation from fertilization and high-throughput tracking.

Objective: To test whether gut microbiota depletion alters anxiety-related, photic, and social behaviors.

Methods: Antibiotic-treated (ABX) larvae (n = 50) were reared in a broad-spectrum cocktail, with depletion confirmed by culture and 16S rRNA sequencing; conventionally colonized (CV) larvae served as controls. At 5 dph, automated open field (OFT; thigmotaxis/center occupancy), dark/light preference, and social preference tests were conducted.

Results: ABX larvae exhibited reduced thigmotaxis (229.72 ± 127.49 s vs. 556.30 ± 291.18 s; $p < 0.05$), increased center occupancy (670.28 ± 127.45 s vs. 343.72 ± 291.18 s; $p < 0.05$), and higher angular velocity (2563.60 ± 96.99 deg/s vs. 2421.61 ± 858.09 deg/s; $p < 0.05$) **versus** CV, with no differences in total distance, swimming speed, or dark/light and social tests ($p > 0.05$).

Conclusion: Depletion selectively attenuated anxiety-like exploration without affecting phototaxis or social responses, suggesting a behavior-specific role for microbiota-gut-brain signaling during early neurodevelopment. Off-target effects cannot be excluded, warranting rescue experiments. The model's transparency could facilitate neural mapping and hypothesis generation on conserved pathways.

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GUT MICROBIOTA-IMMUNE SIGNALING IN FETAL GROWTH RESTRICTION ASSOCIATED WITH MATERNAL COLITIS

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Introduction: Inflammatory bowel disease (IBD) during pregnancy is associated with fetal growth restriction (FGR). Elevated inflammatory cytokines, including interleukin-22 (IL-22), and alterations in the gut microbiota have been reported in pregnant women with IBD. However, the mechanisms linking intestinal inflammation and FGR remain unclear.

Materials and Methods: Pregnant C57BL/6 mice received 2% dextran sulfate sodium (DSS) from embryonic day (E) 9.5 to E14.5 and were analyzed at E17.5. Fetal and placental phenotypes, placental inflammatory and vascular gene expression, AhR and IL-22 signaling, gut microbiota composition, and microbial metabolites were evaluated.

Results: DSS-treated mice exhibited significantly reduced fetal weight without increased post-implantation embryo loss. Placental weight was unchanged, whereas placental inflammatory signaling was enhanced with increased expression of *Flt1* and *Angpt2*. Gut microbiota composition was altered, including reduced *Lactobacillus* abundance. Placental *Cyp1a1* expression was transiently reduced during mid-gestation, suggesting altered AhR signaling.

Conclusion: Maternal intestinal inflammation induced FGR and was associated with placental inflammatory and vascular alterations. Changes in gut microbiota composition and AhR-related signaling suggest a potential role for the gut microbiota-placenta axis in FGR development.

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THE ROLE OF LYPD8 IN HOST DEFENSE AND MICROBIOTA REGULATION IN THE GASTRIC MUCOSA

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Lypd8 is a glycosylated GPI-anchored protein produced by epithelial cells that binds to bacterial flagella in the colon, contributing to the maintenance of colonic mucosal homeostasis. However, its role in the stomach remains unclear. We therefore investigated the role of Lypd8 in gastric microbiota and immunity.

Gastric microbiota from wild-type (WT) and Lypd8-deficient (Lypd8 KO) mice were analyzed by 16S rRNA sequencing. Lypd8-associated bacteria were identified, and gastric Lypd8-expressing cells were characterized by single cell RNAseq analysis. Gastric immune cells were also analyzed by flow cytometry.

Lypd8 KO mice showed an altered gastric microbiota, with an increase abundance of *Lactobacillus*. Lypd8 bound to non-flagellated gastric bacteria, suggesting a distinct mechanism from its flagella-dependent function in the colon. Single cell RNAseq analysis further revealed that gastric Lypd8 was expressed by an epithelial cells distinct from that in the colon. In addition, although gastric ILC2 numbers were unchanged in Lypd8 KO mice, GATA3 expression levels was significantly increased.

These findings revealed a previously unrecognized, tissue-specific role of Lypd8 in the stomach, potentially linking regulation of the gastric microbiota to ILC2 function.

SYSTEMATIC MINING AND PRIORITIZATION OF NOVEL PROBIOTIC CANDIDATES FOR POTENTIAL THERAPEUTIC APPLICATION IN TYPE 1 DIABETES

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Introduction: Type 1 Diabetes (T1D) is a rising autoimmune disease. Research shows that gut dysbiosis contributes to T1D pathogenesis, yet probiotic research on T1D remains focused on conventional *Bifidobacterium* and *Lactobacillus*, overlooking phylogenetically distinct taxa with immunomodulatory potential unexplored. This study developed an integrated in silico pipeline combining probiotics mining, causal inference, and functional genomics, establishing a framework for next-generation novel probable probiotic identification.

Material & Methods: An in-house built AI-ML platform ProbML [1], was used for bacterial strain identification, followed by a rigorous multi-tier pipeline. The strains underwent two-sample Mendelian randomization (MR) and whole-genome functional annotation covering essential functional genes, secondary metabolites, CAZymes, and genome-scale metabolic modeling.

Results: Two strains (S1 and S2) were predicted. Whole-genome characterization revealed complete short chain fatty acid pathways in S1, while S2 showed acetate with partial-other pathways; both strains showed no plasmids, prophages, or virulence factors. MR showed S2 had a significant protective association with T1D (IVW OR=0.88, 95% CI 0.78-0.99, p=0.035).

Conclusion: This integrated pipeline provides a systematic approach for prioritizing novel probiotic candidates for T1D, with potential applications across probiotic research areas. Bacterial culturing and T1D mouse model validation studies are ongoing to further experimentally evaluate the probiotic and therapeutic potential.

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MODULATORY EFFECTS OF GUI-ZHI-JIA-SHAO-YAO-TANG ON CITROBACTER RODENTIIUM-INDUCED COLITIS: INSIGHTS FROM GUT MICROBIOME AND METABOLITE PROFILES

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Introduction: *Citrobacter rodentium* infection induces intestinal inflammation and provides a useful model for investigating host–microbiota interactions. This study investigated the modulatory effects of Gui-Zhi-Jia-Shao-Yao-Tang (GJT) on *C. rodentium*-induced colitis in ovalbumin-sensitized mice.

Material & Methods: Ovalbumin-sensitized mice with *C. rodentium*-induced colitis were treated with GJT. Gut microbial community profiling and fecal metabolomic analysis were performed, followed by pathway and integrated microbiome–metabolite analyses.

Results: GJT supplementation altered gut microbiota composition, increasing the relative abundances of potentially beneficial taxa, including Akkermansiaceae and the Prevotellaceae group. Metabolomic analysis identified 23 metabolites, six of which differed significantly among treatment groups. Six metabolic pathways contributed significantly to intergroup variation, with taurine and hypotaurine metabolism showing the most pronounced effect ($p = 0.02$). Integrated analysis demonstrated coordinated changes in microbial composition and metabolic profiles associated with GJT treatment.

Conclusion: These findings suggest that GJT may modulate *C. rodentium*-induced intestinal inflammation through coordinated regulation of the gut microbiota and associated metabolic pathways.

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IMPACT OF A STRATIFIED SYMBIOTIC SUPPORT AND FORGIVENESS THERAPY ON BIOMARKERS IN CATASTROPHIC AND GASTROINTESTINAL BLEEDING PATIENTS

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Introduction: Chronic stress and trauma dysregulates immune-gastrointestinal via the hypothalamic–pituitary–adrenal (HPA) axis. This retrospective study evaluates a dual intervention (forgiveness psychotherapy and nutritional support) on inflammatory biomarkers in 210 patients with cancer or upper and lower gastrointestinal bleeding.

Material & Methods: Forgiveness and depression scales were correlated with biomarkers as C-Reactive protein (CRP) and Neutrophil-to Lymphocyte Ratio (NLR). Patients eliminating sugar/canned foods (18% rejected) were stratified: Group 1: yogurt, Group 2: (yogurt papaya/oats/pecan); Group 3 (Group 2 plus 200g cooked natural cacti, 20g lettuce, 50g carrots).

Results: In the alarm phase (2% of sample) extreme hostility coincided with CRP>100 mg/dl, NLR=5 and 50% of mortality rate (n=2 suicides). Conversely, 49% reached the liberation phase, showing complete bleeding cessation, normal NLR (1-2) and CRP 3 mg/dl. Crosstabulation proved this 49% exactly matched nutritional Group 3.

Conclusion: Emotional resolution deactivates adrenergic stress, while the advanced symbiotic and cytoprotective matrix of Group 3 provides the essential substrates to normalize systemic immune response and repair tissue damage.

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DECODING THE SALIVARY METABOLOME IN POLYCYSTIC OVARY SYNDROME: TOWARDS NON-INVASIVE BIOMARKER DISCOVERY

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Introduction: PCOS (Polycystic Ovary Syndrome) is a complex endocrine and metabolic disorder characterized by hormonal imbalance, insulin resistance, chronic inflammation, and substantial metabolic heterogeneity. Metabolomic profiling provides a powerful approach to identify disease-associated metabolic signatures and discover novel biomarkers for improved PCOS diagnosis and molecular characterization.

Material & Methods: Saliva samples from 222 Qatari women with PCOS and controls were subjected to untargeted-metabolomic profiling. Metabolites were profiled using UPLC–MS/MS coupled to high-resolution Orbitrap mass spectrometry, yielding 687 biochemicals (622 identified and 65 unidentified). Group differences were assessed using the Wilcoxon rank-sum test, with Benjamini-Hochberg FDR correction for multiple comparisons; $P < 0.05$ was considered statistically significant.

Results: Metabolomic analysis identified 10 nominally significant metabolites between PCOS and controls ($P < 0.05$), involving nucleotide, amino acid, peptide, vitamin, and xenobiotic metabolism. PCOS was associated with higher levels of pyroglutamylarginine, 2'-deoxyguanosine, 2'-deoxyinosine, phenylalanylproline, and pyroglutamylglycine, and lower levels of N-methylproline and 3-hydroxystachydrine.

Conclusion: Salivary metabolomic profiling revealed distinct metabolic alterations associated with PCOS, highlighting potential signatures across multiple metabolic pathways. These findings support the potential of salivary metabolites as non-invasive biomarkers for PCOS, warranting validation in larger independent cohorts.

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GUT MICROBIOME REORGANISATION AFTER *HELICOBACTER PYLORI* ERADICATION IN PARKINSON'S DISEASE REVEALS L-DOPA-METABOLISING GENUS ENRICHMENT

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Introduction: *Helicobacter pylori* (*H. pylori*) eradication improves levodopa absorption in Parkinson's disease (PD) [1]; however, the microbiome consequences of antibiotic-based eradication in a dysbiotic PD gut remain uncharacterised, especially the enrichment of *Eggerthella*, which encodes the *dgr* operon for L-DOPA dehydroxylation [2].

Materials and Methods: Paired longitudinal 16S rRNA amplicon sequencing was performed in 41 PD patients: *H. pylori*-negative (HP-Neg, n = 20) and *H. pylori*-positive (HP-Pos, n = 21). HP-Pos patients received eradication therapy. Community analyses used Bray-Curtis PERMANOVA/ANOSIM, paired Wilcoxon tests with Benjamini-Hochberg false discovery rate (BH-FDR) correction, and a five-method consensus biomarker pipeline.

Conclusion: Eradication drove significant community restructuring in HP-Pos patients (PERMANOVA p = 0.001), absent in HP-Neg controls. Post-eradication *Eggerthella* enrichment may offset levodopa absorption gains and warrants monitoring in HP-PD co-management [3].

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BACTERIAL BIOMARKERS FOR QPCR-BASED COLORECTAL CANCER DETECTION

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Introduction: Colorectal cancer (CRC) is one of the most prevalent cancers worldwide, making early screening essential to improve treatment outcomes and reduce mortality (1). Current CRC screening relies on faecal occult blood tests (FOBT), followed by colonoscopy in positive cases. The detection of CRC-associated bacteria represents a promising non-invasive and accurate approach that could complement actual screening (2). In previous work, we identified a set of anaerobic bacteria enriched in CRC patients (3).

Materials and Methods: Here we developed qPCR assays targeting these bacterial taxa in stool samples. Custom bioinformatic pipelines were implemented to identify species-specific genomic regions for probe design targeting these biomarkers. The qPCR assays were then applied to a cohort of 222 stool samples from CRC patients and healthy controls recruited across all public Galician hospitals to assess the presence and abundance of the selected biomarkers. Statistical analyses were performed to create a sensitive predictive model for classifying individuals as healthy or high-risk, refining risk stratification for colonoscopy referral.

Conclusion: Multiplex qPCR assays have been optimised to simultaneously detect the predictive biomarkers, providing a rapid, cost-effective, and non-invasive screening tool for CRC, with the potential to improve early diagnosis and reduce CRC-associated morbidity.

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ASSOCIATION BETWEEN THE SMALL INTESTINAL MICROBIOME AND PERIPHERALLY DERIVED REGULATORY T CELLS

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Introduction: Regulatory T cells (Tregs) are essential for maintaining intestinal immune homeostasis. Gut microbiota and their metabolites are known to promote the differentiation of peripherally derived Tregs (pTregs) in the colon¹; however, their contribution to small intestinal pTregs remains unclear. We investigated how diet-induced changes in the small intestinal microbiota and metabolites affect pTregs.

Material & Methods: C57BL/6JJcl mice were fed either a standard diet (CE-2) or a low-fiber diet (AIN-93G) from 3 to 7 weeks of age. Small intestinal immune cells, microbiota, metabolites, and immune-related gene expression were analyzed by flow cytometry, 16S rRNA sequencing, GC-MS/LC-MS, and qPCR, respectively. Candidate factors were further evaluated by in vivo *Lactobacillus* administration, water-soluble cellulose butyrate (WSCB) supplementation, and in vitro isoLCA treatment.

Results: The low-fiber diet reduced small intestinal pTregs, IL-10 expression, *Lactobacillus* abundance, and butyrate levels, while increasing isoLCA. *Lactobacillus* administration and WSCB supplementation increased pTregs, although butyrate alone could not fully explain these changes. In vitro, isoLCA tended to suppress pTreg differentiation.

Conclusion: Small intestinal pTregs may be regulated by multiple microbiota-derived factors, including promotion by *Lactobacillus* and suppression by metabolites such as isoLCA.

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FROM IDENTIFICATION TO INTERVENTION: GUT MICROBIOME-ENCODED β -GLUCURONIDASES AND THEIR INHIBITION

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Introduction: The gut microbial β -glucuronidases (GUS) reactivate glucuronidated xenobiotics and drugs, leading to intestinal damage and toxicity. However, the population-specific diversity and functional attributes of GUS enzymes remain underexplored. My research aims to identify and characterize new GUS enzymes and to develop inhibitors to alleviate the GUS-mediated drug toxicity.

Material & Methods: In silico mining and classification based on domain and loop architecture, taxonomic profiling and structure modelling of GUS enzymes were performed. A representative GUS panel was characterized using SDS-PAGE, SEC and DLS, followed by in vitro GUS activity and X-ray crystal structure determination. In vitro compound screening, IC₅₀ and kinetic parameters were determined.

Results: Several new GUS proteins were identified and activity of the selected GUS enzymes was confirmed. Notably, GUSs cleaving the glucuronidated form of anti-cancer drug irinotecan were identified. Among them, GUS from gut symbiont *Akkermansia muciniphila* showed a rare monomeric form with a unique loop deciphered by crystal structure. Furthermore, inhibitor screening identified organodiselenides as slow-binding inhibitors with the highest reported potency in nanomolar IC₅₀ against *Escherichia coli* GUS.

Conclusion: This study uncovers novel GUS enzymes expanding structure-function landscape of β -glucuronidases and the discovery of organodiselenides as specific GUS inhibitors aids in microbiome-targeted therapeutic interventions.

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ORAL-GUT MICROBIAL AND METABOLIC ALTERATIONS ASSOCIATED WITH MESALAZINE INTOLERANCE IN ULCERATIVE COLITIS.

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Introduction: The incidence of intolerance to mesalazine, a mainstay treatment for ulcerative colitis (UC), has increased in recent years; however, its biological basis remains poorly understood. Growing evidence suggests that gut microbiota contribute to mesalazine metabolism, while oral-to-gut microbial transmission has emerged as a potential driver of UC pathogenesis. We aimed to characterize microbial and metabolic signatures associated with mesalazine intolerance through integrated analyses of oral and intestinal ecosystems.

Materials & Methods: Fecal and saliva samples were collected from patients with UC. Patients were classified into a mesalazine-intolerant group (n = 10) and a mesalazine-tolerant group (n = 49). Bacterial composition was analyzed by 16S rRNA sequencing, and metabolomic profiling was performed.

Conclusion: Although no significant differences in overall microbial composition were observed between groups (fecal PERMANOVA, $p = 0.86$; salivary PERMANOVA, $p = 0.96$), LEfSe identified 33 fecal and 5 salivary discriminatory taxa. Integrated analyses consistently identified two signatures associated with mesalazine intolerance: increased *Streptococcus salivarius* in both saliva and feces and elevated fecal isovalerate levels ($\log_2FC = +0.96$, $p = 0.010$). These findings suggest that mesalazine intolerance is associated with oral-gut microbial alteration characterized by oral-derived streptococcal pathobionts and microbial protein fermentation.

DIFFERENTIAL EFFECTS OF CRC-ASSOCIATED ANAEROBES ON INFLAMMATORY SIGNALING IN TUMOR AND NORMAL COLON EPITHELIAL CELLS

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Introduction: Colorectal cancer (CRC) is strongly influenced by host–microbe interactions (1–4). However, the differential effects of CRC-associated bacteria on tumor versus normal intestinal epithelium remain poorly understood.

Materials & Methods: We performed RNA-sequencing analysis to characterize the transcriptional responses of tumor (SW480) and normal (CCD 841 CoN) colon epithelial cells following infection with *Fusobacterium animalis* and *Bacteroides fragilis*, two anaerobic bacterial species enriched in stool samples from patients with CRC (5).

Conclusions: RNA-sequencing revealed extensive transcriptional remodeling in both cellular models. Tumor cells exhibited a stronger pro-inflammatory response to infection with both bacterial species, characterized by marked upregulation of chemokines, including CXCL1, CXCL2, CCL2, CCL7, and CCL20. In normal epithelial cells, *F. animalis* predominantly induced interferon-related responses, whereas *B. fragilis* preferentially activated tissue-remodeling programs. Overall, these findings demonstrate that CRC-associated bacteria differentially modulate host transcriptional responses depending on the epithelial context, providing new insights into host–microbe interactions potentially associated with tumor progression.

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A MICROBIOTA-DEPENDENT BILE ACID PROTECTS AGAINST NEUROINFLAMMATION BY CONTROLLING LIPID RAFT ORGANIZATION IN ASTROCYTES

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Astrocytes are central regulators of neuroinflammation, integrating environmental signals and shaping the responses of surrounding neural and immune cells. However, how microbiota-derived metabolites influence these functions remains poorly understood. Here, we identify the secondary bile acid isolithocholic acid (isoLCA) as a potent regulator of inflammatory astrocyte responses. In primary mouse and human iPSC-derived astrocytes, isoLCA suppressed cytokine-induced inflammation independently of canonical bile acid receptors. Instead, isoLCA rapidly reorganized cholesterol-rich membrane microdomains, accompanied by reduced nuclear accumulation of phosphorylated STAT1, suggesting a link between membrane organization and inflammatory signaling. Importantly, the effects of isoLCA extended beyond astrocytes, reshaping their communication with other CNS cells under inflammatory conditions. IsoLCA-treated, cytokine-activated astrocytes shifted microglia away from inflammatory and antigen-presentation programs towards metabolic adaptation and lipid handling. In parallel, neurons exposed to isoLCA-treated, cytokine-activated astrocytes displayed increased synapse number and dendritic spine density, counteracting changes induced by inflammatory astrocytes. Therapeutic isoLCA administration after disease onset in experimental autoimmune encephalomyelitis ameliorated disease severity. This effect was accompanied by lower microglial MHC-II expression and reduced frequencies of GM-CSF⁺ and GM-CSF⁺ IFN γ ⁺ CD4 T cells in both the brain and spinal cord. Together, our findings link astrocyte membrane organization to neuroimmune communication and identify isoLCA as a potential strategy to limit ongoing neuroinflammation.

CONSTIPATION-INDUCED GUT DYSBIOSIS AGGRAVATES ACNE VIA TRYPTOPHAN METABOLITE-MACROPHAGE AHR AXIS

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Introduction: Constipation is believed to exacerbate acne, particularly in Japanese women, but evidence is limited. We examined how constipation-associated gut dysbiosis affects acne-like inflammation.

Material & Methods: Constipation was induced with loperamide (LP) or a low-fiber diet, followed by topical ethyl palmitate (EP) to induce acne-like folliculitis. Gut microbiota, cytokines, immune-cell trafficking, single-cell transcriptomes, and circulating tryptophan metabolites were analyzed. Candidate metabolites were tested in wild-type and Ahr-deficient bone marrow-derived macrophages and injected into EP-treated mice.

Results: Constipation worsened neutrophil-rich folliculitis without intestinal inflammation. LP expanded Clostridiaceae (LDA=7.4), whereas co-housing attenuated inflammation. No systemic cytokine changes or gut-to-skin immune cell migration were detected. Lesional macrophages showed increased aryl hydrocarbon receptor (AHR) activity, and targeted profiling revealed altered proportions of AHR-related tryptophan metabolites. An indole-pathway metabolite X increased with constipation and enhanced palmitic acid-induced macrophage inflammation in vitro through AHR. Conversely, kynurenine-pathway metabolite Y remained unchanged during constipation but suppressed macrophage inflammation through AHR. In vivo, intravenous X administration worsened EP-induced inflammation, whereas Y administration improved it.

Conclusion: Constipation-induced gut dysbiosis aggravates acne-like inflammation by shifting circulating tryptophan metabolites toward pro-inflammatory AHR signaling. Their effect depends on the balance of pro- and anti-inflammatory AHR ligands, not a single metabolite.

COMPREHENSION OF THE MICROBIAL DYNAMICS OF GASTRIC CANCER THROUGH NANOPORE FULL-LENGTH 16S RNA SEQUENCING IN TWO CHILEAN COHORTS

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Gastric dysbiosis has been increasingly associated with gastric cancer progression, although its characterization across disease stages in Latin American populations remains limited. Gastric biopsies and gastrectomy tissues from 83 Chilean individuals from two independent cohorts were analyzed using full-length 16S rRNA nanopore sequencing: the Magellanic (MAGIC) cohort from Punta Arenas, a sub-Antarctic city in southern Chile, and the Biobank of Tissues and Fluids from the University of Chile (BTUCH) cohort from Santiago, Chile. Significant differences in bacterial community composition were observed throughout disease progression and when comparing gastric cancer with non-gastric cancer. The most abundant genera included *Streptococcus*, *Gemella*, *Granulicatella*, *Helicobacter*, and *Veillonella*. Differential abundance analyses identified stage-specific microbial restructuring during gastric cancer progression. Gastric cancer associated dysbiosis was characterized by depletion of genera such as *Bradyrhizobium* and *Acidovorax*, together with strong enrichment of *Lactobacillus* and *Limosilactobacillus*. Correlation analyses identified 34 genera significantly associated with progression, including progressive increase in *Sarcina*, *Lactobacillus* and *Klebsiella*. Distinct microbial community structures were also observed between diffuse and intestinal gastric cancer subtypes. These findings reveal progressive restructuring of the gastric microbiota during carcinogenesis and identify non-*Helicobacter* microbial signatures associated with gastric cancer progression that may contribute to future biomarker discovery and disease stratification strategies.

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PROBIOTICS AND THE GUT-WOUND MICROBIOTA AXIS IN ANORECTAL SURGERY

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Introduction: Anorectal surgery is complicated by pain, bacterial contamination, and delayed wound repair. Perioperative probiotics may modify these outcomes through the proposed gut-wound microbiota axis.

Materials & Methods: PubMed/MEDLINE, Embase, Cochrane Library, and Web of Science were searched for studies published from January 2000 to December 2024. Clinical and mechanistic evidence on probiotics, short-chain fatty acids, macrophage polarization, wound healing, pain, and infection was narratively synthesized.

Results: Two meta-analyses covering 59 randomized trials in gastrointestinal or colorectal surgery reported fewer postoperative infections with probiotics (risk ratios 0.62-0.63) [1,2]. Direct anorectal evidence was absent. Mechanistic evidence indicates that probiotic-associated short-chain fatty acids may reduce inflammatory signaling and favor pro-resolving macrophage phenotypes.

Conclusion: The gut-wound microbiota axis provides a biologically coherent framework for microbiota-targeted perioperative strategies in anorectal surgery, but does not justify routine clinical use.

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BIOTRA CO-CULTURE FERMENTATION AND THE ZORRO EFFECT: A METABIOTIC STRATEGY FOR MICROBIAL ECOSYSTEM MODULATION AND IMPROVED METABOLIC AND INTESTINAL FUNCTION

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Background

Microbial metabolites play a central role in intestinal homeostasis and systemic metabolic regulation. Biotra is a fermentation technology platform designed to harness microbial interactions and generate bioactive metabolite complexes. Its proposed ecological mechanism, termed the Zorro Effect, hypothesizes that fermentation-derived metabolites can modify nutrient availability and microbial competition, potentially limiting conditions favorable to opportunistic bacteria such as *Klebsiella pneumoniae* while supporting beneficial organisms such as *Akkermansia muciniphila*. This study evaluated the clinical effects of a Metabiotic formulation integrating prebiotics, probiotics and postbiotic metabolites.

Methods:

A randomized, double-blind, placebo-controlled clinical trial enrolled 42 adults with a body mass index of 30–34.9 kg/m². Participants received either a Metabiotic formulation or placebo for four weeks (n = 21 per group). The formulation combined a daytime fermented algae polyphenol complex with nighttime *Lactobacillus paracasei*, *L. plantarum*, *L. fermentum* and *A. muciniphila*-derived postbiotic metabolites. Outcomes included fecal short-chain fatty acids (SCFAs), systemic inflammatory and oxidative stress biomarkers, bowel function and body weight.

Results:

Acetate and butyrate increased significantly versus placebo (both $p < 0.0001$), while propionate was unchanged ($p = 0.9059$). hs-CRP and MDA decreased (both $p < 0.0001$), and TAC increased ($p < 0.0001$). Bowel movement frequency increased ($p < 0.0001$), with improved stool consistency ($p < 0.05$). Body weight decreased significantly versus placebo ($p < 0.0001$). No treatment-emergent adverse events were reported. The coordinated improvements in SCFA profiles, inflammatory and oxidative stress biomarkers, and intestinal function are consistent with enhanced microbial–host metabolic interactions. These findings provide a clinical foundation for investigating Biotra's proposed Zorro Effect. However, microbial species abundance, nutrient redistribution and direct competition between *K. pneumoniae* and *A. muciniphila* were not evaluated. The contribution of co-culture fermentation itself was also not isolated in this trial.

Conclusion:

Four weeks of Metabiotic supplementation significantly improved microbial metabolite profiles, systemic metabolic biomarkers and intestinal function in adults with increased metabolic risk. Biotra's co-culture fermentation approach and proposed Zorro Effect offer a mechanistic research direction for investigating nutrient-mediated microbial ecosystem modulation. Future studies integrating metagenomics, metabolomics, microbial competition assays and isotope-based nutrient tracing are required to validate this mechanism and establish its contribution to clinical outcomes.

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A FERMENTED TURMERIC METABOLITE COMPLEX MODULATES THE GUT–LIVER AXIS: EFFECTS ON GUT MICROBIOTA, SHORT-CHAIN FATTY ACIDS, SYSTEMIC INFLAMMATION, AND LIVER FUNCTION: EVIDENCE FROM TWO RANDOMIZED, DOUBLE-BLIND, CONTROLLED TRIALS

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Introduction:

The gut and liver communicate continuously through the portal vein, biliary tract, and systemic mediators, forming the gut–liver axis¹. Gut microbial composition, short-chain fatty acid (SCFA) production, and intestinal barrier function shape the inflammatory and oxidative load reaching the liver, making this axis a strategic target for preserving metabolic and hepatic health, particularly in overweight adults. Curcuminoids from turmeric (*Curcuma longa*) act on central nodes of this axis, including NF-κB and Nrf2 signalling, but poor absorption, rapid metabolism, and rapid systemic elimination have limited their clinical impact². Using the Ayabiome platform, we applied controlled microbial fermentation to turmeric rhizome to produce Aya® FTE (Fermented Turmeric Extract), a unique turmeric metabolite complex containing pre-formed reduced curcuminoids such as tetrahydrocurcumin, designed for enhanced solubility and bioavailability. Two randomized trials evaluated its effects at the gut and liver ends of the axis.

Methods:

Both trials were randomized, double-blind, parallel-group studies conducted at Medica Tokyo Laboratories, Tokyo, Japan, using Aya® FTE 500 mg/day. In the gut trial, 54 adults aged 25–55 years with mild digestive discomfort were assigned 1:1 to FTE or an equal dose of non-fermented turmeric extract (TE) for 12 weeks; outcomes included the Gastrointestinal Symptom Rating Scale (GSRS), fecal *Lactobacillus* spp., *Bifidobacterium* spp., and *Faecalibacterium prausnitzii* (qPCR), fecal SCFA (GC-FID), serum hs-CRP and 8-OHdG, and plasma superoxide dismutase (SOD). In the liver trial, 60 overweight adults aged 30–55 years (BMI 25.0–30.0 kg/m²) were assigned 1:1 to FTE or matched placebo for 8 weeks; outcomes included ALT, AST, γ-GTP, total bilirubin, and body composition. Between-group effects were assessed by baseline-adjusted ANCOVA.

Results:

Groups were comparable at baseline in both trials. In the gut trial, FTE increased *Lactobacillus* (3.98-fold; $p < 0.0001$), *Bifidobacterium* (3.24-fold; $p = 0.0041$), and *F. prausnitzii* (3.09-fold; $p < 0.0001$) versus TE. Fecal butyrate rose 23.1%, from 12.42 ± 0.74 to 15.29 ± 1.08 μmol/g, and total SCFA rose 15.5% (both $p < 0.0001$), while GSRS total score decreased 18.1% ($p < 0.0001$). Systemically, hs-CRP decreased 18.6% ($p = 0.0080$), 8-OHdG decreased 18.1% ($p < 0.0001$), and SOD activity increased 19.6% ($p = 0.0084$); equal-dose TE produced no significant change in any microbiota, SCFA, inflammatory, or oxidative stress marker. In the liver trial, FTE reduced ALT by 14.7%, from 36.70 ± 6.49 to 31.37 ± 6.12 U/L, γ-GTP by 14.7%, and AST by 7.2% (all $p < 0.0001$ vs placebo), and total bilirubin by 3.7% ($p = 0.0081$), with all values within the normal reference range. Body fat decreased 5.1% and waist circumference by 3.22 cm (both $p < 0.0001$), with lean body mass preserved. No serious adverse events occurred, and tolerability was comparable between groups in both trials.

Conclusion:

Aya® FTE produced convergent improvements across both ends of the gut–liver axis: enrichment of beneficial and butyrate-producing bacteria, increased SCFA output, lower systemic inflammation and oxidative DNA damage, and improved liver function biomarkers and central adiposity. These findings are consistent with a proposed pathway in which SCFA-supported barrier integrity and curcuminoid-metabolite NF-κB inhibition and Nrf2 activation reduce the inflammatory and oxidative burden reaching the liver. Superiority over an equal dose of non-fermented turmeric extract demonstrates that fermentation, not curcuminoid dose alone, drives the gut-level benefits.

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NEUROACTIVE METABOLITES PRODUCED BY A NATIVE BACTERIAL STRAIN ISOLATED FROM WILD EQUATORIAL CACAO: EFFECTS ON NEUROPLASTICITY, COGNITIVE PERFORMANCE, AND FUNCTIONAL BRAIN CONNECTIVITY IN MILD COGNITIVE IMPAIRMENT

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Introduction:

Neurodegenerative disorders, including Alzheimer's disease and other dementias and Parkinson's disease, are increasing rapidly as populations age, creating a particularly urgent challenge in Japan and other developed countries. More broadly, neurological conditions have become the leading cause of disease burden and disability worldwide, emphasizing the need for interventions that preserve brain function before irreversible neurodegeneration develops. We investigated the microbial ecology of wild cacao from an equatorial ecosystem and identified native bacterial isolates capable of biotransforming cacao flavanols, aromatic amino acids, and other natural substrates into metabolites with neuroactive potential. A selected cacao-native *Lactiplantibacillus plantarum* strain, BSG-21, was subsequently used in a controlled precision-fermentation process to produce SynaBiome, a metabolite complex designed to support neuronal energy regulation, BDNF-linked synaptic remodeling, mitochondrial function, and neural connectivity. This randomized trial evaluated its effects on cognition and molecular and electrophysiological indicators of neuroplasticity in adults with mild cognitive impairment.

Methods:

Forty adults aged 50-65 years were enrolled in an 8-week, randomized, double-blind, placebo-controlled, parallel-group trial and assigned 1:1 to SynaBiome 500 mg/day or matched placebo. Cognitive performance was assessed at baseline and Week 8 using the Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Serum brain-derived neurotrophic factor (BDNF), resting-state EEG fronto-parietal connectivity, theta power, safety, and tolerability were also evaluated. Between-group effects were assessed using baseline-adjusted comparisons.

Results:

The groups were comparable at baseline. After 8 weeks, SynaBiome increased MMSE scores from 24.1 ± 2.3 to 27.1 ± 2.2 , representing a 12.4% improvement, while placebo remained unchanged (between-group $p = 0.000029$). ADAS-Cog decreased from 7.1 ± 1.2 to 5.2 ± 1.2 , a 26.8% improvement relative to baseline ($p = 0.000001$). Serum BDNF increased by 34.2% to 25.1 ± 3.7 ng/mL ($p < 0.000001$). These cognitive and neurotrophic changes were accompanied by a 14.5% increase in fronto-parietal connectivity ($p = 0.000098$) and a 29.3% increase in resting-state theta power ($p = 0.000567$), indicating stronger network integration and memory-related neural activity. No serious adverse events occurred, and tolerability was comparable between groups.

Conclusion:

SynaBiome produced convergent improvements across cognitive, neurotrophic, and electrophysiological domains within 8 weeks. The findings provide clinical evidence that precision-fermented cacao metabolites can support neuroplasticity and cognitive resilience rather than transient stimulation. Larger, longer-duration studies should confirm the durability and mechanistic basis of these effects.

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