18TH SEEON CONFERENCE

MICROBIOTA, PROBIOTICS AND HOST

MIKROBIOTA, PROBIOTIKA UND WIRT

JUNE 24TH – 26TH 2026

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CONFERENCE CENTER

Kloster Seeon (Monastery Seeon/ Chiemsee)
Kultur- und Bildungszentrum des Bezirks Oberbayern
Klosterweg 1, 83370 Seeon
www.kloster-seeon.de

SHUTTLE SERVICE DETAILS (BOOKING REQUIRED)

Train station shuttle ~ 30 min
Airport shuttle ~ 1,5 h

Wednesday 24th transfer to Seeon Monastery

13:30 - 15:00	Shuttle from Munich Airport (only for airplane travelers)
14:00 - 14:30	Shuttle from Bad Endorf train station

Friday 26th leaving from Seeon Monastery

13:30	Shuttle departure to Munich airport and Bad Endorf train station

NAVIGATING THE DIGITAL ABSTRACT BAND

In the agenda/ program: The titles of the talks hyperlink to the abstracts. The date in the abstract header hyperlinks to the corresponding day in the agenda/ program.
The poster titles in “Poster session overview” hyperlink to the poster abstracts of each presenter. You can jump back to the poster overview by following the hyperlinked header “POSTER” on the upper lefthand corner of each abstract.

Dear Participants,

Welcome to Kloster Seeon for the 18th Conference on Microbiota–Host Interactions!
This meeting is organised annually by the German Society for Hygiene and Microbiology (DGHM) section "Microbiota, Probiotics and Host." Since its inaugural edition in 2008, the "Seeon Conference" has grown into a vibrant forum bringing together basic and clinical scientists united by a common goal: understanding the human microbiome and its role in health and disease. Lively discussions after talks, during poster sessions, and in the relaxed atmosphere of the Klosterstüberl make this conference a true home for microbiome enthusiasts and newcomers alike.
The conference has a strong track record of shaping the research landscape. Past editions contributed substantially to the establishment of the DFG-funded Priority Programme SPP 1656 "Microbiota – A Microbial Ecosystem at the Edge between Immune Homeostasis and Inflammation," which united over 30 research groups between 2013 and 2019. Since then, microbiome research in Germany has continued to flourish — through Collaborative Research Centres such as CRC1182 "Metaorganisms" (Kiel), CRC1371 "Microbiome Signatures" (Munich), and CRC1382 "Gut–Liver Axis" (Aachen), as well as DFG Clusters of Excellence including "CMFI – Controlling Microbes to Fight Infections" (Tübingen), "Balance of the Microverse" (Jena), and "RESIST – Resolving Infection Susceptibility" (Hannover/Braunschweig), all of which have secured a second funding period. Most recently, a new Priority Programme (SPP2474, "Illuminating Gene Functions in the Human Gut Microbiome") has been launched to shed light on gene functions in the human gut microbiome.
We are therefore especially delighted that the kick-off meeting for SPP2474 will take place here in Seeon, directly preceding the main conference — bringing this exciting new line of work into dialogue with the established consortia that traditionally convene in Seeon to discuss the latest advances in the field.
The conference is also supported by NFDI4Microbiome, which provides the microbiology community with access to data, analysis services, data and metadata standards, and training.
A defining feature of the Seeon Conference is its commitment to young scientists. Each year, the poster slam — in which early-career researchers present their work in short, punchy pitches — has become one of the highlights of the programme, showcasing the creativity and breadth of the next generation of microbiome researchers. Beyond this, we aim to provide a sustainable platform for training and promoting young scientists across a broad range of disciplines, creating space for exchange and collaboration that spans gastroenterology, nutritional medicine, immunology, infection research, microbial ecology, synthetic biology, animal science, and computational biology.
This year's programme features an outstanding lineup of speakers and selected talks. We look forward to stimulating discussions and excellent science. Let's make the most of our time in Seeon!

Prof. Till Strowig and Prof. Lisa Maier, on behalf of the Steering Committee:

Prof. Maria Vehreschild, University Hospital Frankfurt am Main, Germany
Prof. Joel Selkrig, University Hospital of RWTH Aachen, Germany
Prof. Lisa Maier, University of Tübingen, Germany
Prof. Till Strowig, Helmholtz Centre for Infection Research, Braunschweig, Germany

		Wednesday, 24th June 2026
13:30	13:30	departure from Munich Airport
14:00	14:00	departure from Bad Endorf train station
		Room Check-In after 15:00
14:00	16:00	Registration & Coffee
16:00	16:15	Welcoming By Lisa Maier, *Microbiome-Host-Interactions, University of Tuebingen, Germany*
16:15	17:00	**Keynote 1** **Shawna McCallin - Hitting your mark: lessons from the bladder for precision phage therapy** Chaired by Lisa Maier, *Microbiome-Host-Interactions, University of Tuebingen, Germany*
17:00	17:45	Session 1: Spatial Ecology: Who Interacts with Whom Along and Across the Gastrointestinal Tract • ***Short talk 1: Xiaobing Wu*** ***Ectopic colonization by oral bacteria in the small intestine of stunted children*** • ***Short talk 2: Martin Jahn*** ***Spatial ecology determines microbiome function and infection resilience*** • ***Short talk 3: Carmen Paulmann*** ***NFDI4Microbiota: Making Microbiology Data FAIR and Open*** Chaired by Lisa Maier, *Microbiome-Host-Interactions, University of Tuebingen, Germany*
18:15	19:45	Dinner
19:45	21:00	**Poster Pitch (2 minutes/slides)** Chaired by Joel Selkrig, *Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*
21:00		Bowling & Co

		Thursday, 25th June 2026
9:00	9:45	**Keynote 2** **Felix Key - Decoding the zoonotic past of human pathogens** Chaired by Joel Selkrig, *Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*
9:45	10:30	Session 2: Host–Microbiome Interactions in Development and Intestinal Disease • ***Short talk 1: Sophia Adlkirchner*** ***Escherichia coli shapes intestinal B-cell responses and influences susceptibility to Inflammatory bowel disease*** • ***Short talk 2: Jiatong Nie*** ***In-vivo and ex-vivo modelling of a human-derived complex synthetic consortium (hcom2) to study the impact of exclusive enteral nutrition on microbiome functions in Crohn's disease*** • ***Short talk 3: Parag Kundu*** ***Maternal gut microbiota programs Fetal stem cells*** Chaired by Joel Selkrig, *Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*
:30	10:55	**Hot topic 1** **Sarela Garcia-Santamarina - Drug-gut microbiota interactions: from single species to communities** Chaired by Joel Selkrig, *Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*
10:55	11:25	Coffee break/ Poster at first glance
11:25	12:10	**Keynote 3** **Elin Org - Population-based biobanks as a resource for uncovering health–microbiome interactions** Chaired by Lisa Maier, *Microbiome-Host-Interactions, University of Tuebingen, Germany*
12:10	12:35	**Hot topic 2** **Christian Diener - From Metagenomes to Metabolites: A Toolkit for Decoding Gut Niche Dynamics** Chaired by Lisa Maier, *Microbiome-Host-Interactions, University of Tuebingen, Germany*
12:35	14:05	Lunch

14:05	14:30	**Hot topic 3** **Markus Schneider - An oral-gut-liver axis linking periodontitis to steatohepatitis** Chaired by Lisa Maier, *Microbiome-Host-Interactions, University of Tuebingen, Germany*
14:30	15:15	Session 3: Microbial Surface Architecture in the Gut: Structure Meets Function • ***Short talk 1: Ana Paula Schaan*** ***Host Lifestyle and disease status shape diversity and function of gut bacterial extracellular vesicles*** • ***Short talk 2: Jann-Louis Hau*** **Elucidating the structure of the *P. vulgatus* surface layer by in-cell cryo-electron tomography** • ***Short talk 3: Marianne Grognot*** ***Microbiota ANALYSIS by single-cell tracking reveals increased swimming motility and diverse swimming behaviors in the inflamed gut*** Chaired by Lisa Maier, *Microbiome-Host-Interactions, University of Tuebingen, Germany*
15:15	16:00	**Keynote 4** **KC Huang - Ecology and evolution of the gut microbiota** Chaired by Joel Selkrig, *Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*
16:00	16:30	Coffee break
16:30	17:00	DGHM Fachgruppenmeeting for members
18:30	19:30	Dinner
19:30	21:00	**Poster session**
21:00		Bowling & Co

Friday, 26th June 2026

		Room Check-out before 11:00
9:00	9:45	**Keynote 5** **Moran Yassour -TBA** Chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*
9:45	10:45	Session 4: Functional Microbiome Dynamics Across Host Niches • ***Short talk 1: Parab Lavisha*** ***A humanized Galleria mellonella model reveals prophage-mediated breakdown of colonization resistance against Salmonella*** • ***Short talk 2: Johanna Bosch*** ***Functional and Ecological Characterisation of novel SCIFF peptides from the Gut microbiome*** • ***Short talk 3: Mohamed Tarek Badr*** ***Stage-dependent remodelling of the lower airway microbiome in non-small cell lung cancer*** Chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*
10:45	11:15	Coffee break
11:15	11:40	**Hot topic 4** **Jakob Wirbel - Long-read metagenomics reveals phage dynamics in the human gut microbiome** Chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*
11:40	12:00	Awards & Farewell Chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*
12:00	13:15	Lunch
13:30		Shuttle departure from Kloster Seeon

POSTER SESSION OVERVIEW

1	**Stephanie Kuhls**	**Murine and human Natf6 transgenes differentially induce epithelial stress and colonic tumorgenesis**
2	**Leon Becklas**	**Deciphering the role of extracellular nucleotides in microbial communities by targeted LC-MS/MS**
3	**Hristiyana Yancheva**	**Lactic acid bacteria in breast milk and infant feces: Identification and safety profile**
4	**Govindarajan Deepalakshmi**	**Profiling and ex vivo internalization dynamics of lactobacillus-derived extracellular vesicles**
5	**Jan Karpa**	**Sulfate-reducing bacteria in the gut, how they got there, and their role in disease**
6	**Taina Lobo e Silva**	**Screening for solutions: tailoring prebiotics and optimising culture media for gut health research**
7	**Yan Zhu**	**Targeting oxidative stress regulators with antisense oligomers in *Segatella copri* complex**
8	**Youzheng Teo**	**Disentangling the interactions of streptococcus salivarius with the innate immune system of stunted children**
9	**Viliana Miteva**	**Isolation, identification and phenotypic characterization of limosilactobacillus fermentum strains from human breastmilk and infant faeces**
10	**Lynn Schintgen**	**High-fiber diet and time-restricted feeding induce convergent quantitative gut microbiome and anti-inflammatory responses**
11	**Li Pan**	**Temporal dynamics of the chimpanzee microbiome**
12	**Emilja Djukanovic**	**Conditionally expressed proteomes of the oligo-mouse-microbiota across intestinal regions**
13	**Madeleine Drexler**	**The impact of microalgae on the gut microbiome: randomized controlled interventions in asian and caucasian populations**
14	**Michaela Herz**	**The gut microbiome in glioblastoma: a prospective case–control study**
15	**Madita K. Brodmann**	**Intra-gastrointestinal microbiome organization of mice on high-fat or high-fiber diet**
16	**Lucas Moitinho-Silva**	**Global patterns from 180,000 human gut metagenomes**
17	**Anna Baborski**	**Assessing individual colonisation resistance using human-gut-derived microbial communities**
18	**Tim Schmitter**	**Oral care impact of two probiotic strains**
19	**Verena Wiemann**	**Ion-dependent phage decolonization of vancomycin-resistant Enterococcus faecium (VRE) in an in vitro gut model**

20	**Thomas Fließwasser**	**A widespread SCCmec-located gene cluster protects mrsa against toxic polysulfides**
21	**Carolin Fritz**	**Microbial strain persistence along the human gastrointestinal tract**
22	**Daniel Podlesny**	**From fair infrastructure to discovery: nfdi4microbiota enables planetary-scale research**
23	**Dimitris Papagiannidis**	**Multiplexed protein-compound interaction screen unravels an unconventional crp regulator in bacteroides**
24	**Cornelia Gottschick**	**Early childhood high abundance of gut Bacteroides is associated with increased risk for developing ear nose and throat infections and contributes to a high degree of microbiota stability and resilience after dysbiotic events**
25	**Anjali Pattathil**	**Mapping cell-surface protein complexes in Bacteroidales**
26	**Joachim J. Hug**	**Unraveling the arsenal and mechanisms that Bbacteroidetes use for kin competition**
27	**Maja Magel**	**For gut's sake – NFDI4microbiota facilitates sustainable microbiome research**
28	**Sudharsan Govindaraj**	**Establishment of a quantitative screening platform for fiber degradation by gut commensals**
29	**Sara Posadas-Cantera**	**Next-generation sequencing for detection of ascitic fungal infections in surgical icu patients**
30	**Alexander Rechberger**	**Occurrence and characterization of type VI secretion system genes in the human gut microbiota**
31	**Vanessa Norz**	**Determination of oxygen consumptions rates in Segatella copri dsm 18205 using optical oxygen sensors**
32	**Elisa Cappio Barazzone**	**Redefining microbial contributions to nitrogen metabolism in urea cycle disorders**
33	**Lena Amend**	**Bacteroides-mediated glycan processing shapes nutrient availability for an enteric pathogen**
34	**Mara Montag**	**Investigating the influence of context-dependent interactions on the metaproteomic profile of a defined gut bacterial community**
35	**Dilan Nisa Yilmaz Aydog**	**Development of an ex vivo assay to characterize the colonization resistance of human stool samples against enteric pathogens**
36	**Stanimira Ivanova**	**Assessment of the safety and acid stress resistance of lactic acid bacteria from the breast milk and the neonatal gut microbiome**

ABSTRACT COLLECTION

HITTING YOUR MARK: LESSONS FROM THE BLADDER FOR PRECISION PHAGE THERAPY

Shawna McCallin[1]

[1]Department of Neuro-urology, Balgrist University Hospital, University of Zürich, Zürich, CH
[2]Spinal Cord Injury Center, Balgrist University Hospital, University of Zürich, Zürich, CH

The growing appreciation of the human microbiome has transformed how we think about infectious diseases and their treatment. Coupled with the growing concerns of antimicrobial resistance, a real need for therapeutic alternatives have emerged that not only resolve infections but also reduce unwanted side effects, such as microbiome disruption. Bacteriophages, viruses that naturally infect bacteria, offer a unique opportunity to control bacterial pathogens while minimizing disruption to surrounding microbial communities. As interest in phage therapy expands, it has become clear that treatment outcomes are shaped not only by the target pathogen but also by the broader host and microbial ecosystem in which infection occurs.

Urinary tract infections (UTIs), which affect hundreds of millions of people annually, particularly women, and remain one of the leading reasons for antibiotic prescription worldwide, illustrate this challenge well. Bacterial colonization and infection are dynamic processes shaped by microbial community structure, host immunity, mucosal barriers, catheterization, and environmental factors. While broad-spectrum antibiotics are still often effective in resolving infections, an incomplete understanding of these interactions have ultimately led to recurrent infections and the development of multidrug resistance. Precision therapies such as phages, on the other hand, depend on accurately identifying the right pathogen, in the right patient, at the right time.

This lecture will be a crash course in the development of phage therapy and the power of hindsight. Although isolating phages from environmental is relatively straightforward, selection filters important for downstream performance need to be incorporated early into discovery programs to ensure the selection of clinically relevant phages. Our early experiences in treating UTI patients with phages has helped to shed light on realistic expectations for clinical and microbiological outcomes with non-antibiotic treatment strategies, challenging current notions for drug performance metrics. The central challenge for the next generation of antibacterial therapies may not only be discovering better antibacterial agents, but rather understanding the ecological and immunological context in which they must function and how to demonstrate their additional value.

DECODING THE ZOONOTIC PAST OF HUMAN PATHOGENS

Felix M. Key[1]

[1] *Max Planck Institute for Infection Biology, Berlin, Germany*

Prehistoric zoonotic spill overs are the root cause for many human infectious diseases known today, which have shaped human evolution in the past and will influence us and our society in the future. Reconstructing pathogen genomes using ancient DNA from animal remains offers a timely and unique opportunity to investigate prehistoric reservoirs of pathogens and their spatiotemporal emergence as well as transmission and adaptation to the human host. However, compared to the established field of human-associated paleomicrobiology, differences in the life history of (domesticated) animals, as well as their postmortem treatment and archeological deposition, affect the chances to recover ancient zoonotic pathogen DNA from animal remains. Here I present recent advances in the utilisation of prehistoric animal remains for reconstructing ancient pathogen genomes and how it informs us about past human-animal interactions enabling the rise of infectious diseases. By highlighting both the challenges and opportunities of this nascent field, I aim to motivate further research into the past of microbes and their interaction with the human host.

POPULATION-BASED BIOBANKS AS A RESOURCE FOR UNCOVERING HEALTH–MICROBIOME INTERACTIONS

Elin Org[1]

[1] *Estonian Genome Centre, Instutitute of Genomics, University of Tartu, Estonia*

Biobanks characterized by deep phenotyping and both retrospective and prospective data collection represent a transformative resource for microbiome science. By integrating longitudinal data, it is possible to characterize the long-term impact of past exposures on the microbiome, while simultaneously identifying microbial biomarkers for future disease risk and predictors of medication in-target and off-target effects. We have showed in the Estonian Micobiome Cohort (EstMB; N ~ 3000) that the effect of a broad range of medication, including antibiotics and several non-antibiotic human-targeted medications, such as psycholepstics, antidepressants, proton pump inhibitors, and beta-blockers, remain detectable years after use and showing cumulative, additive patterns. Thus, past exposures such as long-term medication use can be an important and often overlooked determinant of gut microbiome composition, and the effect of past exposures might be severely underestimated. Beyond clinical records, population-based data collections can facilitate multi-omic integration studies and the generation of population-specific references. Our research shows that *de novo* generation of population-specific metagenome-assembled genomes and reference can identify cohort-specific associations, which can remain undetected using global references. Our ongoing endeavors further suggest that combining microbiome data with host genetic predisposition, as measured by polygenic risk scores, can uncover novel disease mechanisms and explain significant inter-individual variability. Collectively, the maturation of large-scale biobanks and longitudinal frameworks is expected to advance microbiome science and move microbiome research closer to clinical utility, providing the foundation for precision interventions and improved diagnostic accuracy.

DRUG-GUT MICROBIOTA INTERACTIONS: FROM SINGLE SPECIES TO COMMUNITIES

Sarela Garcia-Santamarina[1], Michael Kuhn[2], Saravanan Devendran[2], Lisa Maier[3], Marja Driessen[2], André Mateus[4], Eleonora Mastrorilli[2], Ana Rita Brochado[3], Mikhail M. Savitski[2], Kiran Patil[5], Michael Zimmermann[2], Peer Bork[2], Nassos Typas[2]

[1] *Deep Microbiome Metabolomics, Leibniz-HKI, Germany*
[2] *EMBL Heidelberg, Germany*
[3] *Eberhard Karls University of Tübingen, Germany*
[4] *The Laboratory for Molecular Infection Medicine Sweden, MIMS, Sweden*
[5] *University of Cambridge, United Kingdom*

Pharmaceuticals can directly inhibit the growth of gut bacteria, but the degree such interactions manifest in complex community settings is an open question. Here we leveraged a human colon 32-species synthetic community to compare the effects of 30 drugs with their effects on each community member in isolation. While most individual drug–species interactions remained the same in the community context, communal behaviors emerged in 26% of all tested cases. Cross-protection, during which drug-sensitive species became protected in community, was 6-times more frequent than cross-sensitization, the converse phenomenon.

Cross-protection decreased and cross-sensitization increased at higher drug concentrations, suggesting that the resilience of microbial communities can collapse when perturbations get stronger. By metabolically profiling drug-treated communities, we showed that both drug biotransformation and bioaccumulation contribute mechanistically to communal protection. As a proof-of-principle, we molecularly dissected a prominent case: species expressing specific nitroreductases degraded niclosamide, thereby protecting both themselves and sensitive community members.

Building on these findings, we are expanding our synthetic communities' framework to new physiological contexts with the integration of organ-on-chip and metabolomics to functionally dissect drug-microbiome-host interactions in physiologically relevant host contexts.

FROM METAGENOMES TO METABOLITES: A TOOLKIT FOR DECODING GUT NICHE DYNAMICS

Christian Diener[1]

[1]Diagnostic and Research Institute of Hygiene, Microbiology and Environmental Medicine, Medical University of Graz, Austria

Throughout the human lifespan, the gastrointestinal tract is colonized by a distinct microbial community shaped by host lifestyle and diet. This results in a unique gut microbiome shaped by our varying lifestyles and diets. Within this ecosystem, microbes navigate complex networks of nutrient competition and metabolic co-dependencies. This ecological complexity remains a primary hurdle for microbiome-targeted therapies. Microbial composition alone rarely predicts realized niches or metabolic outputs without accounting for the specific metabolic environment and emergent trophic interactions.

To address this, we present an integrated framework for quantifying dietary intake directly from metagenomic data and applying microbial community metabolic modeling to map niche dynamics in healthy and perturbed gut microbiota. By estimating dietary compounds from metagenomic reads, we successfully monitored participant compliance in intervention studies and characterized dietary variability across diverse human cohorts. Furthermore, our community-scale metabolic models provided mechanistic insights into how dietary fibers modulate short-chain fatty acid (SCFA) production and how probiotic interventions alter pathogen engraftment *in vivo*. By pairing model predictions with high-throughput *ex vivo* anaerobic cultivation, we established a robust pipeline for screening intervention efficacy in a risk-free, physiologically relevant environment.

This synergy of environmentally aware computational methods and *ex vivo* validation provides a rapid, scalable toolkit for predicting personalized intervention outcomes with applications in the design and engineering of next-generation microbiome therapeutics.

AN ORAL-GUT-LIVER AXIS LINKING PERIODONTITIS TO STEATOHEPATITIS

Astrid Devriese[1, 2, 4], Shahrzad Ghadirzad[1], Qusay Salih[3, 4, 5], Madhuri Haque[1, 3, 4, 5], Till Robin Lesker[6], Mohammed Alatter[1], Maria Backhaus[1, 3, 4, 5], Lu Jiang[1], Julius Jaeger[1], Mohamed Ramadan Mohamed[1], Mona Peltzer[1], Sara Setlaoui[2], Yunus Emre Kılıçkıran[4], Christian Trautwein[1], Theresa Hildegard Wirtz[1], Maike Rebecca Pollmanns[1], Raphaela Staltner[7], Ina Bergheim[7], Agata A. Bielecka[6], Nikolaus Gaßler[8], Julia Wollenhaupt[9], Heidi Noels[9], Joachim Jankowski[9], Marta Rizk[10], Sihem Brenji[10], Rogerio B. Craveiro[10], Michael Wolf[10], Marek Weiler[11], Fabian Kiessling[11], Carolin V. Schneider[1], Till Strowig[6, 12], Stefan Wolfart[2], Taskin Tuna[2] and Kai Markus Schneider[1, 3, 4, 5, 13, *]

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[13]*Lead contact, *Presenting Author*

Background & Aims: Periodontitis is linked to metabolic dysfunction–associated steatotic liver disease (MASLD), but causality and mechanisms remain unclear. We investigated mechanisms by which periodontal inflammation drives MASLD progression via an oral-gut-liver axis.

Methods: We combined population-based data from ~500,000 UK Biobank participants, a deeply phenotyped prospective clinical cohort, and mechanistic mouse models. Participants underwent liver- and dental-related phenotyping, blood testing, and periodontal examinations. In mice, periodontitis was induced by silk ligatures and combined with a Western-style diet (WSD) to model MASLD. Flow cytometry, transcriptomics, protein assays, imaging, and 16S rRNA gene amplicon sequencing interrogated oral and gut microbiota, barrier integrity, hepatic inflammation, and fibrosis.

Results: In mice, periodontitis aggravated WSD-driven MASLD, increasing hepatocellular injury, steatosis, immune infiltration, and collagen deposition. Periodontitis reshaped the oral microbiome, induced gut dysbiosis, impaired intestinal barrier function, and promoted bacterial translocation along the oral-gut-liver axis, evidenced by increased hepatic bacterial signatures and enhanced oral-gut microbial overlap. This phenotype was amplified by gastric acid suppression (PPI) and blunted by broad-spectrum antibiotics, while cohousing equalized gut communities and abolished liver phenotype differences. Hepatic bacterial burden correlated with activation of fibroinflammatory pathways, including an IL-17–linked immune program and extracellular matrix remodeling signatures consistent with stellate cell activation and progressive fibrogenesis. In humans, periodontitis was associated with higher liver disease burden and fibrosis risk in UK Biobank, and in the clinical cohort coincided with oral and gut microbiome alterations, increased oral-gut overlap, and biochemical features of more severe hepatic dysfunction.

Conclusion: Periodontitis is a causal, microbiome-dependent driver of MASLD progression via an oral-gut-liver axis that promotes barrier dysfunction, microbial translocation, and IL-17– mediated fibroinflammation. Periodontal care, and potentially oral/gut microbiota modulation, may mitigate MASLD progression.

LONG-READ METAGENOMICS REVEALS PHAGE DYNAMICS IN THE HUMAN GUT MICROBIOME

Jakob Wirbel[1,2], Angela S. Hickey[3], Daniel Chang[3], Nora J. Enright[4], Mai Dvorak[5], Rachael B. Chanin[2], Danica T. Schmidtke[6], Ami S. Bhatt[2]

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[6]*Department of Microbiology and Immunology, Stanford University, CA, USA*

Bacteriophages can profoundly impact microbial ecology and health, especially in the context of the human gut microbiome. However, the dynamics of gut phages has been challenging to study: short-read sequencing often results in fragmented assemblies of phage genomes, virus-like particle sequencing potentially misses integrated prophages, and the information about host bacteria is unavailable for most phages. Here, we used deep long-read bulk metagenomic sequencing to track prophage dynamics in stool samples from six healthy individuals, sampled 2 years apart. Long-read sequencing resulted in the detection of a higher proportion of integrated phages, in line with theoretical expectations about phage lifestyle in the gut, and recovered more complete phage genomes than short-read sequencing. Most phages remained stably integrated into the same host, yet approximately 5% of phages were dynamically lost or gained from persistent bacterial hosts. Through the detection of structural variations, we observed phage induction at predominantly low levels (1-3 times coverage compared to the surrounding host region) and the coexistence of hosts with and without a given prophage within the same sample. While most prophages in our dataset were integrated into the same bacterial species, we found multiple instances when the same phage was integrated into bacterial of different taxonomic families, challenging the notion of narrow host-specificity. Finally, we discovered a novel group of phages that co-opt IS30 transposases for their mobilization, representing an intriguing example of phage domestication of selfish, bacterial-derived genetic elements. In summary, our findings illuminate fundamental aspects of phage-bacteria dynamics in the human gut microbiome and illustrate the power of long-read metagenomic sequencing for biological discovery.

Associated publication:
Wirbel*, Hickey*, *et al.* Long-read metagenomics reveals phage dynamics in the human gut microbiome. **Nature** 649, 982–990 (2026). https://doi.org/10.1038/s41586-025-09786-2

ECTOPIC COLONIZATION BY ORAL BACTERIA IN THE SMALL INTESTINE OF STUNTED CHILDREN

Xiaobing Wu, Johann Mignolet, Carla Hernández-Cabanyero, Youzheng Teo, Vincent de Bakker, Jan-Willem Veening, Pascale Vonaesch

Department of Fundamental Microbiology, University of Lausanne, Lausanne, Switzerland

Stunting, characterized by impaired growth and development in children who are low height-for-age, stands as the most prevalent manifestation of childhood undernutrition worldwide. However, effective treatments for stunting remain elusive, with even the most promising strategies having only little influence on growth retardation and associated pathophysiological disruptions. Several studies have suggested a link between Environmental Enteric Dysfunction (EED), a syndrome characterized by chronic inflammation of the small intestine, small intestinal oral bacterial overgrowth (SIOBO) and childhood stunting.

Within the Afribiota project, a large collection of bacteria from the upper gastrointestinal tract of stunted children has been established. *Streptococcus salivarius* represents the largest proportion of the isolates, reflecting its high prevalence of S. salivarius in SIOBO.

In this study, we aim to assess the colonization factors that favor the colonization and overgrowth of *S. salivarius* in the small intestinal tract of mice using a CRISPRi screening approach and to compare the colonization potential of S. salivarius between different strains as well as in the context of healthy or undernourished mice or mice suffering from EED. Analyses show a strain-dependent potential of *S. salivarius* to colonize the murine intestinal tract, with overall log 2-3 stronger colonization in undernourished mice according to both fecal and small intestinal samples. Of all the isolates that have been tested, S. salivarius AF111 was observed to demonstrate the most effective colonization capability, of which a CRISPRi library is designed and constructed. Furthermore, an in vivo CRISPRi library assay of a reference *S. salivarius* strain revealed 98 essential genes for colonization and overgrowth in the mouse small intestine, although clear bottleneck effects were observed, particularly in the small intestinal samples. Future works include complementing these results with in vitro CRISPRi screening with rich and undernourished media.

We expect from this study a better understanding of the main genetic factors favoring the overgrowth of *S. salivarius* in the intestinal tract of undernourished mice and mice suffering of EED, thus paving the way for the development of treatments able to prevent SIOBO in stunted children in the future.

SPATIAL ECOLOGY DETERMINES MICROBIOME FUNCTION AND INFECTION RESILIENCE

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The spatial arrangement of species is fundamental to the structure and function of ecosystems, yet our understanding of spatial ecology in the gut, one of the most significant microbiomes, remains limited. Here, we introduce spatial functional genomics for human gut bacteria to characterise their spatial distribution and how it shifts during infection in a mouse model. Our findings uncover fundamental principles governing the spatial organisation within the mammalian gut. We observe that species distributions are influenced by their habitats, where similar species tend to cluster around shared resources, and by metabolic interactions among species. Infection with *Salmonella enterica* serovar Typhimurium alters the spatial ecology and highlights a connection between spatial positioning and ecological success: species that are centrally positioned in health proliferate while peripheral species decline. Additionally, we demonstrate that our spatial network metrics are much more effective in predicting inflammation severity than traditional fecal diversity measures. Overall, our research indicates that the gut microbiota is highly organised in space, following ecological principles driven by nutrient availability, species interactions, and host factors.

NFDI4MICROBIOTA: MAKING MICROBIOLOGY DATA FAIR AND OPEN

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NFDI4Microbiota is a consortium within the DFG-funded German National Research Data Infrastructure (NFDI) that focuses on managing, standardizing, and sharing microbiological and microbiome-related research data. Its mission is to enhance data accessibility, interoperability, and reproducibility for researchers working with microbiota across diverse domains, including health, agriculture, and the environment.

The vision of NFDI4Microbiota is to enable microbiology researchers to translate research data into a deeper understanding of microbial species and their molecular interactions. To achieve this, the consortium aims to serve as central hub for supporting the microbiology community through access to data, analysis services, data and metadata standards, and training. NFDI4Microbiota actively promotes the FAIR (Findable, Accessible, Interoperable, and Reusable) principles and Open Science. NFDI4Microbiota supports microbiology researchers throughout the entire research lifecycle (from study design to data publication) by providing tools, infrastructure, and expert guidance that ensure data are FAIR and reproducible. The consortium develops and offers computational infrastructure and analytical workflows for storing, accessing, processing, and interpreting diverse microbiology-related data types. Secure, scalable object storage (ARUNA) combined with guided metadata templates ensures consistent recording of technical and biological metadata. For data analysis, NFDI4Microbiota provides standardized, containerized workflows (CloWM), software tools, and access to curated databases. A comprehensive Knowledge Base offers training materials and best practices, while a dedicated helpdesk provides personalized consultation on all aspects of data management and analysis. In addition, NFDI4Microbiota organizes training courses covering topics such as metaomics, programming, research data management, and electronic lab notebooks. To engage with early-career researchers, the consortium established an ambassador program that helps identify community needs. All relevant information and services are available through the NFDI4Microbiota web portal: https://nfdi4microbiota.de/

In conclusion, NFDI4Microbiota is building a robust data infrastructure to advance microbiome research, following its guiding principle: Making Microbiology Data FAIR and Open.

ESCHERICHIA COLI SHAPES INTESTINAL B-CELL RESPONSES AND INFLUENCES SUSCEPTIBILITY TO INFLAMMATORY BOWEL DISEASE

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Escherichia coli (Ec) is an early pioneer colonizer of the neonatal gut, yet how it shapes mucosal immune development in early life remains poorly understood. Ec is frequently enriched in individuals with Inflammatory Bowel Disease (IBD), where it can outcompete other commensals during colitis. Although the metabolic mechanisms underlying this competitive advantage are well characterized, the role of early-life mucosal immune priming in influencing later IBD susceptibility is unclear. We recently demonstrated that neonatal Ec colonization drives the accumulation of B-cells in Peyer's patches through curli, amyloid fibers that are essential for biofilm formation and epithelial adhesion, and by engaging Toll-like receptor 2. Curli-deficient Ec strains failed to elicit this response, revealing a previously unrecognized role for microbial amyloids in shaping early-life mucosal immunity. Here, we investigate how Ec-mediated immune imprinting during the early-life window of opportunity influences susceptibility to experimental IBD.

Specific-pathogen-free wild-type (wt), IL-10$^{-/-}$, and B-cell-deficient μMT mice were colonized at birth with either curli-proficient or curli-deficient commensal or probiotic Ec strains, or maintained Ec-free. To disentangle Ec-driven immune imprinting from colitis-induced Ec blooms, a subset of mice received streptomycin to permanently eliminate Ec following neonatal colonization. Subsequently, wt and μMT mice were subjected to dextran sulfate sodium (DSS)-induced colitis, whereas IL-10$^{-/-}$ mice were monitored for spontaneous colitis development. Disease severity was evaluated by weight loss, colonic shortening, histopathology, and flow-cytometric immune profiling.

Early-life exposure to curli-expressing Ec conferred robust protection against DSS-induced colitis, whereas Ec-naïve mice or those primed with curli-deficient strains showed heightened disease susceptibility. Curli-expressing Ec induced tolerogenic B- and T-cell responses, which were markedly reduced in Ec-naïve mice and in those colonized with curli-deficient Ec.

Early-life colonization with curli-expressing Ec establishes a durable, B-cell- and IL-10-dependent immune imprint that enhances resistance to colitis, indicating a key role for curli-mediated mucosal tolerance. Future work using neonatal isolates with defined curli expression will clarify whether neonatal Ec strain identity shapes long-term IBD susceptibility.

IN-VIVO AND *EX-VIVO* MODELLING OF A HUMAN-DERIVED COMPLEX SYNTHETIC CONSORTIUM (HCOM2) TO STUDY THE IMPACT OF EXCLUSIVE ENTERAL NUTRITION ON MICROBIOME FUNCTIONS IN CROHN'S DISEASE

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Exclusive enteral nutrition (EEN) is the first-line therapy for inducing remission in pediatric patients with mild-to-moderate Crohn's disease (CD). Our previous prospective pediatric cohort (n=20) was conducted to characterize the function of microbiome changes of treatment-naïve CD patients in response to EEN. Metagenomic analysis on longitudinally collected stool samples reflected highly individualized patient-specific variations in response to the treatment, limiting our ability to mechanistically investigate EEN-associated microbiome signatures through colonization experiments in mice. Consequently, in collaboration with Prof. Michael Fischbach from Stanford University, we introduced a human-derived complex synthetic consortium with 119 strains (hcom2) as a model microbiota with defined composition to explore the protective mechanisms of dietary treatment in inflammatory bowel disease (IBD).

Metagenomics sequencing data demonstrated that we have successfully established a stable hcom2-like (hcom-l) community (80-99 strains) using germ-free (GF) C57BL/6 mice over multiple generations, which serve as a reproducible microbial source for further colonization experiments in gnotobiotic IBD mouse models. Furthermore, *ex-vivo* cultivation of the hcom2-l community using continuous gut chemostats mimicking human colon conditions led to a reduced microbial richness (67-84 strains) but created a specific niche for certain bacterial taxa such as *Bacteroides ovatus, Bacteroides uniformis* and *Enterocloster bolteae.* To investigate the microbe-host interactions in response to the EEN treatment, GF *Il10*$^{-/-}$ mice were colonized with hcom2-l for 4 weeks. Histopathological examination of the colon Swiss rolls indicated that the consortium triggered inflammation in the *Il10*$^{-/-}$ mice receiving chow diet, but not in the *Il10*$^{-/-}$ mice receiving an EEN-like fiber-free diet. Further characterization of an *ex-vivo* modified hcom2-l using an EEN-like media in the continuous gut chemostat is currently ongoing. In summary, our study demonstrates that *in-vivo* and

ex-vivo modelling of the hcom2 community facilitates mechanistic investigations into a dietary treatment in IBD within a complex defined microbial environment.

MATERNAL GUT MICROBIOTA PROGRAMS FETAL STEM CELLS

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The maternal microbiome is a critical determinant for child health. However, its impact on offspring's stem cells, which regulate development, remains poorly understood. To understand the role of maternal microbiome in conditioning the offspring's stem cells, we manipulated maternal microbiota. Different maternal microbiomes had distinct effects on proliferation and differentiation of stem cells in the offspring's gut and brain, influencing their developmental-trajectory, physiology and long-term health. Transplantation of altered maternal-microbiota into axenic mice transmitted these stem cell traits to the recipients' offspring. Metabolically more active maternal microbiomes enriched the levels of circulating SCFAs and amino acids leaving distinct transcriptomic imprints on cellular pathways of offspring's stem cells. These results suggest a fundamental role of maternal microbiome in programming fetal stem cells and represent a promising target for interventions.

HOST LIFESTYLE AND DISEASE STATUS SHAPES DIVERSITY AND FUNCTION OF GUT BACTERIAL EXTRACELLULAR VESICLES

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Bacterial extracellular vesicles (BEVs) are produced by bacteria in the gut and act as key mediators of bacterial communication, carrying diverse molecular cargo across the intestinal lumen and physiological barriers. Yet, it remains unclear how BEV taxonomic and functional diversity is structured across hosts and influence host-microbiome interactions. Here, we employed a multi-omics approach to characterize the molecular diversity of BEVs from stool samples of global populations and an inflammatory bowel disease cohort, as well as BEVs derived from a subset of gut bacterial isolates. We found that (i) a broad diversity of gut bacteria produces BEVs in the gut, (ii) BEV cargo proteins map to functions that vary with host lifestyle, disease status, and bacterial taxonomy; and (iii) BEVs interact with host-derived proteins, including intestinal immunoglobulins. Ongoing assays aim to investigate the role of BEVs in mediating microbial competition in the gut ecosystem and to which extent they can elicit host immune responses. Overall, our data reveal BEVs as key modulators of host–microbiome interactions.

ELUCIDATING THE STRUCTURE OF THE P. VULGATUS SURFACE LAYER BY IN-CELL CRYO-ELECTRON TOMOGRAPHY

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Phocaeicola vulgatus is one of the most prevalent species in the human gut microbiome. At the interface between the competitive gut environment and the bacterial cell, surface biomolecules modulate the interaction of *P. vulgatus* with the host, other microbes and phages. Of particular importance are surface layers (S-layers), paracrystalline protein assemblies that surround the cell and confer multiple functions including structural integrity, protection from phages and extreme environments, and evasion from the host immune system. In Bacteroides species, especially in *P. vulgatus*, key aspects of the S-layer biology remain elusive. These include its structure, constituent proteins, the associated protein interaction network, mechanism of membrane attachment, and physiological functions. We describe the use of cryo-electron tomography to demonstrate the presence of an S-layer in *P. vulgatus* cells. Subtomogram averaging resolves the *P. vulgatus* S-layer structure in the native context of the cell, and together with (crosslinking) proteomics data and structure prediction, enabled the identification of the core S-layer protein and integrative structural modeling of its oligomeric assembly. Understanding of the S-layer structure helps elucidate how *P. vulgatus* interacts with its host and the environment, including for nutrient acquisition, and defends against phages.

MICROBIOTA ANALYSIS BY SINGLE-CELL TRACKING REVEALS INCREASED SWIMMING MOTILITY AND DIVERSE SWIMMING BEHAVIORS IN THE INFLAMED GUT

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Many bacterial species can express flagella, enabling diverse swimming behaviors[1] to reach favourable environments. However, direct assessment of commensal bacteria motilities in the healthy and diseased gut is lacking.

Using a stain-free high-throughput 3D tracking method[2], we assessed the motility of individual bacterial cells (i) directly in gut samples, as well as (ii) in pure cultures of commensal isolates from the Human Intestinal Bacteria Collection (HiBC[3]).

In fresh samples taken along the intestinal tract of healthy mice, less than 3% of bacteria displayed swimming motility. Up to a 12-fold increase in the fraction of motile bacteria was observed in four mouse models of gut inflammation: IBD ($IL10^{-/-}$ mice), PSC-IBD ($Mdr2^{-/-}$ mice with DSS-induced colitis), *Salmonella enterica* serovar Typhimurium infection, and high-fat diet. Most swimming behaviours differed from the classical run-tumble motility of model organism *Escherichia coli*. Further analysis of these swimming behaviours suggests a strong selection for low number of flagella per motile cell. Increased oxygen levels, often associated with inflammation, triggered or enhanced the motile fraction in 6 of 9 isolates tested *in vitro*.

This work provides a novel and quantitative perspective on gut microbiota dynamics under healthy and inflamed conditions.

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A HUMANIZED GALLERIA MELLONELLA MODEL REVEALS PROPHAGE-MEDIATED BREAKDOWN OF COLONIZATION RESISTANCE AGAINST SALMONELLA

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Colonization resistance from the gut microbiota is a critical barrier to pathogen invasion, but in vivo studies are constrained by the cost and complexity of vertebrate models. Here, we developed a humanised *Galleria mellonella* infection model by inoculating wax moth larvae with complex human fecal microbiota. 16S rRNA gene sequencing confirmed stable, reproducible establishment of a diverse human-associated community across larvae over four days. Humanised larvae exhibited colonization resistance to *Salmonella enterica* serovar Typhimurium (*S.* Typhimurium), with mortality reduced to 20% compared with 90% in non-colonised controls. To test whether prophages can overcome this barrier, we infected larvae with isogenic *S.* Typhimurium strains differing only by presence of prophage P22. Infection with the P22-carrying strain caused a threefold increase in larval mortality (60% vs. 20% with the prophage-free strain), higher pathogen loads, and a significant reduction in resident *Escherichia coli* abundance. Free P22 virions were detected early after infection, indicating lysis of susceptible resident bacteria. Notably, phage resistance evolved rapidly within resident *E. coli*, with the proportion of P22-susceptible clones declining from 62.5% to 29.2% over four days. Infection by prophage-carrying *Salmonella* perturbs microbiome composition. *Salmonella* became the dominant genus after infection, displacing commensals like *Agathobacter*, *Bifidobacterium, Bacteroides, Blautia* and *Escherichia–Shigella*. These findings suggest that prophage-mediated enhancement of pathogen invasion is transient—facilitating early infection until resistance emerges in the microbiota. Temperate prophages might act as self-replicating invasion factors that break down microbiome-derived colonization resistance (*in-vivo*). To our knowledge, this is the first humanised *G. mellonella* model supporting complex human microbiota. This scalable, low-cost platform enables mechanistic dissection of pathogen–phage–microbiota interactions relevant to human gut ecology.

FUNCTIONAL AND ECOLOGICAL CHARACTERISATION OF NOVEL SCIFF PEPTIDES FROM THE GUT MICROBIOME

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Microbial natural products are highly diverse bioactive molecules. Functional studies of those produced in the human gut microbiome are needed. In previous work, we identified a novel group of small SCIFF peptides in cultured bacteria from the pig gut microbiome. Genomic analysis of 675 isolates from multiple host species (human, n = 340; mouse, n = 212; pig, n = 123), revealed that 177 strains encoded the corresponding biosynthetic gene cluster (BGC) and all belonged to the phylum *Bacillota*. The prevalence of SCIFF precursor peptides across 9,634 human gut metagenomes was >10% for 109 of the 177 strains, with up to 66.78% for *Maccoyia intestinihominis*. Amino acid sequence comparison revealed 2 dominant peptide clusters, one of which included none of the so-far described sacti- or ranthipeptides and only isolates of the genus *Clostridium sensu stricto*. These peptides shared a conserved motif, with 6 cysteines within 27 amino acids (SCIFF domain). To investigate their ecology and function's role in a targeted manner, we selected the SCIFF peptide encoded by *Clostridium beijerinckii* DSM 105335, which can be genetically modified. Targeted qPCR showed that the precursor peptide of *C. beijerinckii* was mainly expressed during mid-exponential growth phase, similar to other antimicrobial peptides like steptosactin. A knockout mutant of this strain, ΔrSAM, unable to produce the mature SCIFF peptide due to deletion of the radical S-adenosylmethionine (rSAM) enzyme was created by ClosTron mutagenesis. To find possible microbiome members affected by the specialized peptide, the growth of commensal isolates was tested in the presence of culture supernatant from the wildtype and mutant strain. Out of 12 strains tested, the butyrate producer *Roseburia intestinalis* DSM 14610^T was sensitive, *i.e.* its growth was significantly reduced by cell-free supernatants from the wildtype but not the ΔrSAM strain. Testing of other *R. intestinalis* isolates revealed the antimicrobial effect to be strain specific towards DSM 14610^T, one additional strain, JCM 31262, displayed a reduced sensitivity to the cell-free supernatant, whilst the growth of 2 other strains was not affected. Co-cultivation experiments confirmed these findings. A defined microbial community of cultured bacteria was developed to study the relevance of the novel SCIFF peptide *in vitro*. Serial batch fermentation experiments revealed a difference in relative abundances of *C. beijerinckii* WT and ΔrSAM within the community (25.6 % vs. 6.8 % after 5 daily transfers). Proteomic analysis showed significant changes in protein expression not only in the *C. beijerinckii* strains but also in other members of the defined microbial community, suggesting an influence of the SCIFF peptide on *C. beijerinckii's* metabolism and strain dynamics during community growth. These findings are being tested further using stool-derived *in vitro* communities.

STAGE-DEPENDENT REMODELLING OF THE LOWER AIRWAY MICROBIOME IN NON-SMALL CELL LUNG CANCER

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Introduction

Emerging evidence suggests that the lung microbiome plays a significant role in respiratory health and disease; however, its relationship with lung cancer remains insufficiently explored. This study aimed to characterise the lower-airway microbiome in lung cancer patients and to evaluate its associations with tumor stage, smoking history, and clinical phenotypes.

Patients and Methods

We conducted a single-centre prospective study analysing paired bronchial lavage (BL) samples from patients with suspected or proven lung cancer. Paired bronchial lavage samples were collected during bronchoscopy from the affected lobe and the contralateral lobe. Demographic data as well as clinical information (smoking history, FEV1, lung lesion site, and presence of contralateral lesions on CT scan) were collected from medical records at admission. Patients with history of systemic corticosteroids and/or immunosuppressive therapy in the last 12 months before enrolment, history of systemic antibiotics for any reason in the last 4 weeks before enrolment, or history of chemotherapy and/or radiation were excluded. Microbial DNA was extracted and sequenced using culture-independent 16S rRNA amplicon sequencing. Alpha diversity was assessed using Shannon and inverse Simpson indices. Bioinformatics tools, including LEfSe and MaAsLin2, were used to identify associations between bacterial features and clinical phenotypes.

Results

We performed bacterial amplicon sequencing on paired bronchial lavage samples from 119 patients with suspected lung cancer, of whom 96 were confirmed to have lung cancer (87 non-small cell lung cancer (NSCLC), 9 small cell lung cancer (SCLC)), and 16 had benign disease. We identified a consistent lower airway microbial “core” dominated by *Bacillota*, *Bacteroidota*, and *Actinomycetota*, with *Streptococcus* and *Prevotella* as predominant genera. Microbial community composition was largely similar between affected and contralateral lung lobes. Overall diversity did not distinguish benign from malignant disease, certain taxa -including *Micrococcus* and *Streptococcus*- were

enriched in cancer samples. Within NSCLC, microbial diversity increased with advancing tumor stage, particularly in patients with lymph node or systemic metastases, and was accompanied by enrichment of *Streptococcus mitis*, *Corynebacterium*, and *Veillonella*. In contrast, smoking exerted a strong diversity-reducing effect, with α-diversity inversely correlating with cumulative exposure. Notably, never-smoker NSCLC patients displayed enrichment of *Streptococcus*, *Veillonella*, and *Prevotella*.

Conclusion

The similarity in microbial community composition between affected and contralateral lung lobes supports the presence of a global rather than lobe-specific airway microbiome. This study demonstrates that the lower-airway microbiome undergoes stage-dependent alterations in NSCLC, driven predominantly by nodal and systemic metastases.

MURINE AND HUMAN NATF6 TRANSGENES DIFFERENTIALLY INDUCE EPITHELIAL STRESS AND COLONIC TUMORIGENESIS

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Colorectal cancer (CRC) is among the most common and lethal malignancies. Activated transcription factor 6 (ATF6)-driven epithelial endoplasmic reticulum (ER)-stress signaling can contribute to CRC development. Our established nATF6^{IEC} and nATF6xVil-Cre^{ERT2} models, which constitutively or inducibly overexpress the murine active form of ATF6 (nATF6) in intestinal epithelial cells (IECs), develop spontaneous colonic tumors. To investigate human-specific ATF6-dependent mechanisms, we generated mouse models expressing human nATF6 (hnATF6) in IECs. This study examines the *in vivo* effects of hnATF6 and compares them with the established murine models.

Survival under chronic or inducible hnATF6 expression was assessed. Tumor onset, number, size, and distribution were monitored longitudinally. ER-stress responses of IECs were evaluated by Grp78 staining. Epithelial proliferation was quantified by anti-Ki67 staining, goblet cell numbers by PAS/AB staining, and microbiota composition by 16S rRNA sequencing.

In contrast to the established models, only inducible expression of hnATF6 in hnATF6xVil-Cre^{ERT2} mice was tolerated, whereas chronic constitutive expression of hnATF6 resulted in lethality. nATF6^{IEC} and nATF6xVil-Cre^{ERT2} mice developed tumors with 100% incidence by 12 weeks of age or 15 weeks after tamoxifen induction in the proximal-mid colon, whereas hnATF6xVil-Cre^{ERT2} mice exhibited hyperplasia in the mid-distal colon in 50% of animals 20 weeks after tamoxifen treatment. Ki67 and PAS/AB staining revealed model-dependent epithelial alterations. Grp78 staining showed distinct ER-stress patterns: murine nATF6 drove uniform epithelial induction, whereas hnATF6 expression resulted in focal increases limited to subsets of crypts. The gut microbiota of nATF6^{IEC} mice was altered prior to tumor onset. In hnATF6xVil-Cre^{ERT2} mice, the gut microbiota showed a transgene-dose-dependent shift with expansion of the *Lachnospiraceae NK4A136 group* and depletion of core colonizers ASF356 and unclassified Lachnospiraceae.

In conclusion, murine and human nATF6 transgenes exert distinct effects on colonic tumorigenesis in mouse models, indicating species-specific differences in ATF6-driven tumor development.

DECIPHERING THE ROLE OF EXTRACELLULAR NUCLEOTIDES IN MICROBIAL COMMUNITIES BY TARGETED LC-MS/MS

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Microbiome–host interactions rely on diverse metabolic exchanges, yet the functional relevance and scope of microbially derived nucleotide-mediated processes remain poorly defined. To address this gap, we established a targeted LC-MS/MS workflow quantifying over 40 purine- and pyrimidine-related metabolites including 19 nucleotides, 12 nucleosides and 7 nucleobases. Combined with a custom H-cell co-cultivation system, this platform enables species-resolved analysis within the SIHUMIx gut model community, supporting the investigation of nucleotide occurrence, community dynamics, and potential cross-feeding interactions. Addressing the chemical lability of nucleotide triphosphates (XTP), we optimized workflows to maximize XTP recovery. For supernatants, cold methanol–water extraction with sonication provided sufficient matrix effect reduction and superior analyte preservation compared to SPE; furthermore, freeze-drying markedly reduced artificial XDP formation. For intracellular metabolomics, quenching in water–glycerol followed by freeze–thaw cell disruption in liquid nitrogen with a methanol–water solvent yielded the highest XTP extraction from cell pellets. Using these protocols, single-species profiling revealed species-specific and growth-phase-dependent extracellular nucleotide patterns. For instance, *T. ramosa* and *C. butyricum* exhibited highly similar exometabolomic fingerprints – with low early-growth-phase nucleotide levels shifting to broad accumulation in the late exponential phase – differing only in the secretion of NADP (*T. ramosa*) versus CTP (*C. butyricum*). This contrasted strongly with *B. thetaiotaomicron*, which only showed NAD accumulation. These distinct fingerprints underscore the need for species-resolved studies and further elucidation of the regulation of intracellular syntheses and secretion. However, these data furthermore provide the foundation for genome-based metabolic modelling and exo-metabolome focused therapeutic strategies.

LACTIC ACID BACTERIA IN BREAST MILK AND INFANT FECES: IDENTIFICATION AND SAFETY PROFILE

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Key words: lactic acid bacteria, breastmilk, infant faeces, Bulgarian mothers and infants

Lactic acid bacteria (LAB) are valued in the food and pharmaceutical industries for their GRAS (Generally Recognized as Safe) status and prolonged use. As components of breast milk and the newborn gastrointestinal tract, they shape the early intestinal ecosystem. This study isolated, identified, and characterized cultivable LAB, mainly lactobacilli, from breast milk and infant fecal samples of mother-child tandem pairs. Seventy isolates were identified by MALDI-TOF MS, with taxonomic affiliation confirmed by 16S rRNA analysis. Species found included *L. paracasei, L. rhamnosus, L. fermentum, L. reuteri, L. plantarum, L. gasseri, L. buchneri, E. faecalis, and E. faecium*. Safety properties, such as DNase and haemolytic activity, were evaluated; all strains were non-haemolytic and DNase negative. The phenotypic antibiotic susceptibility of the strains to 15 antibiotics was determined by disk diffusion method. PCR analyses of resistant strains identified blaZ, aac(6')aph(2"), aph(3")-IIIa, parC, and tetM resistance genes. Some *E. faecalis* and *E. faecium* strains contained agg, asaI, gelE, and esp virulence genes.

In conclusion, this study expands knowledge of cultivable lactic acid bacteria in breast milk and infant fecal samples from Bulgarian donors. Most identified strains belong to g. Lactobacillus, highlighting their key role in the formation of the early intestinal microbiota.

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PROFILING AND *EX VIVO* INTERNALIZATION DYNAMICS OF LACTOBACILLUS-DERIVED EXTRACELLULAR VESICLES

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Keywords: Bacterial Extracellular vesicles, murine colonic organoids, internalization, host interaction

Bacterial extracellular vesicles (BEVs) serve as critical mediators in bacteria-host interactions, functioning as specialized delivery systems that shuttle biomolecules into host cells to reprogram signalling cascades and physiological processes. Despite evidence that BEVs can regulate host immune responses, there is still a significant knowledge gap concerning their interaction with and penetration of the colonic epithelial layer, which serves as the primary barrier of the gastrointestinal mucosa. The present study focusses on uptake and permeability of BEVs from *Limosilactobacillus reuteri* (LR) and *Lactiplantibacillus plantarum* (LP) into the murine based colonic organoid. LR and LP bacteria were isolated from different sources but stemming from the same family of *Lactobacillaceae*. a key commensal gut microbe. Both of these bacteria were reported to exhibit immunomodulatory properties and gut barrier strengthening in eukaryotic host. The internalization rate was considerably higher with LRderived BEVs into the murine colonic epithelium preferably via endocytotic pathways than the LP BEVs. Increased cellular adhesion of LR BEVs may be attributed to the difference in the zeta-potential measurements between LR BEVs and LP BEVs. The isolation and characterization of LR and LP derived BEV according to MiSEV guidelines, 2024 reveals similar morphological properties and different physiochemical properties between BEVs. Also, functional relevance into the *ex vivo* model of colonic organoids suggests the protective role of LR and LP BEV.

SULFATE-REDUCING BACTERIA IN THE GUT, HOW THEY GOT THERE, AND THEIR ROLE IN DISEASE

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Global incidence rates for inflammatory bowel diseases (IBD) are rising, mirroring patterns of westernization. Although the exact etiology is not yet fully understood, many risk factors such as genetic predispositions, diet, and lifestyle have been shown to play a role in disease onset and progression. With the rise of multi-omics approaches, growing evidence highlights changes in the structure of the microbial community, i.e., dysbiosis, as a critical contributor. Among the altered microbial taxa, sulfate-reducing bacteria (SRB) have increasingly been detected as differentially abundant when comparing disease groups. During SRB overgrowth, hydrogen sulfide (H_2S) and acetate levels in the intestine are significantly elevated, influencing not only microbial composition but also the integrity of the gut epithelial barrier. All SRB described in humans belong to the family of *Desulfovibrionaceae*, with the majority falling under the genus *Desulfovibrio*. These bacteria usually thrive in nutrient-rich, anoxic environments such as marine sediments or wastewater, using sulfate (SO_4^{2-}) as a terminal electron acceptor. Considering the gut is a significantly more competitive ecosystem, *Desulfovibrio* spp. would have had to evolve mechanisms for metabolic and physiological flexibility.

To investigate specific adaptations enabling their presence in the gut, we want to use a comparative genomics approach to examine genomes of *Desulfovibrio* spp. from environmental habitats and the human gut. For example, first analyses have revealed that species in environmental habitats, on average, harbor fewer prophages than those found in the gut. Adding another layer of depth, those comparisons will be extended to genomes of *Desulfovibrio* spp. found in the fecal material of IBD patients to investigate possible changes during disease. In parallel, we will isolate *Desulfovibrio* spp. from the fecal material of healthy and diseased patients to characterize their contribution to the gut environment by analyzing transcriptome, proteome, and metabolome. Finally, by integrating these multi-omics data and applying them to multi-modal deep learning models, we aim to find disease-specific fingerprints paving the way for novel therapeutic interventions in IBD.

SCREENING FOR SOLUTIONS: TAILORING PREBIOTICS AND OPTIMISING CULTURE MEDIA FOR GUT HEALTH RESEARCH

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The rise of multidrug-resistant (MDR) bacteria is a growing threat to global health, driven in part by the misuse of antibiotics and their impact on the gut microbiota. Antibiotics disrupt the gut ecosystem by reducing microbial diversity, compromising colonisation resistance, and creating niches that favour opportunistic pathogens, including MDR strains. Prebiotics, non-digestible substrates that stimulate beneficial microbes, provide a strategy to restore microbiota function and enhance resistance to colonisation. However, previous studies have shown moderate effects, with the presence of non-responders, likely due to the use of single compounds and inter-individual variability.

Here, we propose a three-phase study using a high-throughput *ex vivo* screening platform to identify and optimise prebiotic strategies across different populations. In phase 1, prebiotics will be screened for their ability to improve microbiota resilience upon antibiotic exposure. Phase 2 will evaluate their capacity to suppress or eradicate MDR bacteria, specifically Enterobacterales. Phase 3 will apply findings from the *ex vivo* work in a proof-of-principle study in humans.

A critical step in this workflow is ensuring that the *ex vivo* system accurately represents the original gut community. Faecal cultures are susceptible to compositional bias, and certain media formulations can promote the disproportionate expansion of fast-growing taxa, particularly members of the Pseudomonadota, which can outcompete strict anaerobes, reduce diversity, and compromise the ecological fidelity and interpretability of the model.

We evaluated four media: modified Gifu Anaerobic Medium (mGAM), Bryant and Burkey medium (BB), and two hybrid formulations (BG and GB), each tested with and without a mucin layer to better mimic the gut mucosal environment. Using faecal samples from healthy infants and adults (n=2 per group) with distinct diets, we assessed how well each condition preserved the baseline community, limited Pseudomonadota overgrowth, and maintained mucosa-associated taxa. Community shifts were measured using qPCR targeting the five major gut phyla.

In adults, clear inter-individual variation was observed alongside medium effects, highlighting the need to minimise variability in the model. Despite this, media BG and BB limited within-donor compositional shifts (Bray–Curtis 0.04 – 0.06) and showed the greatest consistency across donors.

Infant microbiota varied less between individuals, with BB emerging as the most consistent medium (within-donor Bray–Curtis 0.14). Mucin had minimal impact on infant microbiota but, in adults, led to an increase in the relative abundance of Actinomycetota, with 1.3 – 5.3 fold-changes across donors.

Though the specific taxa driving this effect could not be understood at the phylum level, future 16S rRNA gene sequencing will help to better characterise these compositional changes. Together, these optimised conditions provide a more reliable and representative basis for *ex vivo* faecal culture, facilitating the study of downstream prebiotic interventions.

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TARGETING OXIDATIVE STRESS REGULATORS WITH ANTISENSE OLIGOMERS IN SEGATELLA COPRI COMPLEX

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The genus *Segatella* (formerly *Prevotella*) includes abundant members of the human microbiota, whose prevalence and relative abundance have been linked to host diet and lifestyle. In particular, the *S. copri* complex (ScC), comprising 13 genetically and functionally diverse clades, is strongly positively associated with fiber-rich diets. Intriguingly, industrialization appears to not only reduce the abundance of ScC in the gut microbiome but may also actively select for specific phenotypes in this ancient group of microbes, such as enhanced oxygen tolerance.

Our recent findings showed that a lineage of modern *S. copri* isolates encodes a LysR-family transcriptional regulator OxyR, which is induced by oxygen and associated with enhanced oxygen tolerance, suggesting a role in gut colonization and host-to-host transmission under transient oxygen exposure. Conversely, PerR is a Fur-family transcriptional repressor, which is ubiquitously present and evolutionarily conserved in *Segatella*. Inactivation of *perR* induces an oxidative stress response in *S. copri* and decreases gut colonization efficiency. Despite their likely roles in oxidative stress response, the broader functions of PerR and OxyR across diverse members of the ScC, as well as their potential roles in adapting to different gut ecosystems influenced by host lifestyle and diet, remain underexplored.

Given the genetic intractability of many *Segatella* species and strains, we applied antisense oligomers (ASOs) as a non-genetic gene-silencing approach across different members of the ScC, targeting *perR* or *oxyR* in this work. Targeting *perR* with 10 µM ASO conjugated to the $(RXR)_4XB$ peptide recapitulated the growth delay phenotype of the *perR* deletion mutant in *S. copri* HDD04. Similarly, ASO-mediated knockdown of *oxyR* in the *oxyR*-positive strain RPA01 inhibited growth, indicating that OxyR might be important for growth in this strain and that protein-level suppression is effective. Using this approach, we are currently investigating the roles of PerR and OxyR in oxidative stress in the ScC in models of gut microbiome colonization and transmission.

DISENTANGLING THE INTERACTIONS OF STREPTOCOCCUS SALIVARIUS WITH THE INNATE IMMUNE SYSTEM OF STUNTED CHILDREN

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Chronic undernutrition can lead to stunted child growth, a condition resulting in cognitive delays and a weakened immune response. Stunting affects approximately 100 million children under 5 globally, with the highest prevalence in low- and middle-income countries. Stunted children suffer from small intestinal bacterial overgrowth characterized by an overabundance of oral bacteria (SIOBO), in particular, *Streptococcus salivarius*. Moreover, this overgrowth is associated with both intestinal and systemic inflammation. Thus, contrary to previous reports, where *S. salivarius* is broadly used as a probiotic for its anti-inflammatory properties, it might instead be contributing to gut dysbiosis and an elevated inflammatory response in undernourished children.

To elucidate this hypothesis, we screened 35 *S. salivarius* isolates from the upper gastrointestinal tract of stunted children for their inflammatory potential and show that the strains vary in their capacity to induce IL-6, where 23 out of 35 strains were classified as potentially inflammatory. Co-culturing small intestinal epithelial cells, TLR2, and NOD2 reporter cells with the bacteria and their components, we delineate that the inflammatory potential is at least partially independent of NOD2 activation and is associated with a heat-labile component of the bacterial cell wall. We further characterized the cell surface structures through electron microscopy, peptidoglycan profiling and whole-genome sequencing. Comparative genomics revealed that variations within the serine-rich repeat locus (SRR) and the capsular polysaccharide locus (cps) were associated with the potential to activate NOD2. The *cpsY* mutant did not lead to a change in the ability to activate NOD2. However, targeted mutants of specific SRR glycoproteins confirm the association between the absence of surface glycoproteins and the loss of NOD2 activation. Ongoing work is focused on assessing the molecular mechanism mediating NOD2 activation and the potential of *S. salivarius* to interact with further innate immune pathways.

Ultimately, to a better understanding of the host-small intestinal microbe interactions and the underlying molecular mechanism will help design new strategies to prevent small intestinal disorders and stunting in undernourished children.

ISOLATION, IDENTIFICATION AND PHENOTYPIC CHARACTERIZATION OF *LIMOSILACTOBACILLUS FERMENTUM* STRAINS FROM HUMAN BREASTMILK AND INFANT FAECES

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Keywords: breastmilk, gastrointestinal tract, LAB, *Limosilactobacillus fermentum*

Lactic acid bacteria (LAB) are a diverse group of bacteria widely distributed in both environmental sources and the human body, especially in the gastrointestinal tract (GIT), playing a crucial role in the host's health and development from early life. LAB are highly persistent in human breastmilk (HBM) and through transmission during breastfeeding, they colonize the infants' GIT. *Limosilactobacillus fermentum* is a frequently isolated species from HBM and infant faeces and reported as a probiotic due to its diverse functional and health – promoting properties. Our investigation was focused on the abundance of *L. fermentum* in HBM and infant faeces from Bulgarian samples of mothers and their newborns tandem pairs. Classical microbiological methods and the MALDI–TOF SM technique were applied for the isolation and identification of the target species. Phenotypic characterization was performed by observing the colony morphology. The species identity was confirmed by conventional species-specific PCR analyses. The results showed that *L. fermentum* strains are abundant in 27% of the potential LAB isolates. A total of 54 from 214 strains, originating from both HBM and infant faeces, were identified as *L. fermentum*. Macromorphologically, the strains were characterized with smooth, creamy-white, round, and medium-sized colonies in 95% of the isolates. Micromorphologically, cells were elongated, slender, and rod-shaped, occurring as a single cell and/or in pairs and short chains. The identity of the *L. fermentum* species, determined by MALDI-TOF SM, was 100% confirmed by species-specific PCR analysis.
Overall, our investigation revealed that *L. fermentum* is highly abundant in both human breastmilk and infant faeces as one of the most common species for the Bulgarian cohort, with a possible transmission route from mother to newborn.

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HIGH-FIBER DIET AND TIME-RESTRICTED FEEDING INDUCE CONVERGENT QUANTITATIVE GUT MICROBIOME AND ANTI-INFLAMMATORY RESPONSES

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The gut microbiome has been implicated in a wide range of human disorders. However, reported associations between fecal taxonomic microbiota and disease remain inconsistent across studies, cohorts, and interventions. These observed discrepancies can be partly explained with the compositional nature of microbiome data, in which a shift in relative abundance of one taxon inevitably alters the composition of the entire community. To address the limitations of purely relative abundance-based microbiome analysis, several quantitative approaches have emerged in recent years, including qPCR or flow cytometry-based assays capable of determining absolute microbial abundances, both at the community and single-taxon levels. Here, we expanded a food dye-based gastrointestinal (GI) passage assay, originally intended to measure GI transit time, to simultaneously quantify absolute microbiota proliferation (fecal microbiota excretion), total stool production (fecal mass) and fecal microbiota density (fecal microbial load) in mice of distinct genetic backgrounds subjected to different diets and feeding patterns. We demonstrate that these quantitative gut microbiome parameters (QMP) are differently modulated by diet composition, feeding pattern, and IL10- deficiency. A high-fiber diet (HFiD) and time-restricted feeding (TRF) both reduced GI transit time and drove convergent reductions in microbiota excretion and microbial load, whereas a high-fat diet (HFaD) induced opposing effects on these parameters. Correlation analyses identified longer GI transit time as the primary driver of increased microbiota excretion and microbial load, but not fecal mass. Furthermore, QMP alterations were associated with similar intestinal gene expression signatures, consistent with anti-inflammatory effects previously attributed to HFiD and TRF. In contrast, fecal taxonomic microbiota profiles were confounded by ecological and experimental variables, showing limited reproducibility across experiments. The convergent QMP and gene expression responses observed across mechanistically distinct dietary and feeding interventions, despite highly heterogeneous compositional microbiome backgrounds, may help explain previously reported inconsistencies in microbiome-disease associations, and point to an overlooked diagnostic and therapeutic utility of quantitative microbiome parameters.

TEMPORAL DYNAMICS OF THE CHIMPANZEE MICROBIOME

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Bacterial strains within a species can exhibit substantial genetic variation and play an important role in shaping the composition and resilience of gut microbial communities. Understanding strain-level dynamics is therefore essential for characterizing microbial dynamics in the gut. However, the long-term patterns of strains within a host and their response to environmental factors, host characteristics, and social interactions remain poorly understood. In this study, we investigated strain-level dynamics across a seventeen-year longitudinal dataset from eighteen wild chimpanzees. By integrating multiple strain-resolved approaches, we show that great apes commonly harbor multiple strains of the same species, with no sinlge strain consistently dominating. Species with fewer strains tend to exhibit greater strain stability within host. Furthermore, while we observe seasonal variation at the genus and species levels, social interactions play a more dominant role than seasonality in shaping strain-level patterns among hosts. Consistently, genetic distances between samples are more similar among individuals within the same social group. These results suggest that social transmission plays a central role in maintaining strain diversity and may contribute to long-term stability.

CONDITIONALLY EXPRESSED PROTEOMES OF THE OLIGO-MOUSE-MICROBIOTA ACROSS INTESTINAL REGIONS

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The Oligo-Mouse-Microbiota (OMM12) is a defined synthetic bacterial community that stably colonizes the murine gut and captures the characteristics and biological features of the murine microbiota. Here, we present preliminary community proteomics data from OMM12-colonized germ-free mice, obtained from small intestine, cecum and colon samples. Global proteome profiling reveals pronounced region-specific shifts in community protein expression, with subsets of conditionally expressed proteins detected only in particular gut regions, indicating distinct and highly localized functional states of OMM12 along the gastrointestinal tract. Previous studies and our own preliminary data provide evidence for metabolic cooperation within the community, e.g. member-specific exchange of metabolites such as amino acids and nucleobases. We aim to mechanistically resolve the interaction networks, specifically regarding amino acid metabolism and cross-feeding within the community. We will use differential isotope labelling by amino acids (DILAC) in defined co-culture and community experiments by supplying selected isotope-labelled amino acids and quantifying label incorporation into strain-resolved proteomes to distinguish amino acid producers from consumers and to map metabolic exchange routes. This combined proteomics framework will provide a mechanistic insight into amino acid exchange and metabolic cooperation in a synthetic gut community.

THE IMPACT OF MICROALGAE ON THE GUT MICROBIOME: RANDOMIZED CONTROLLED INTERVENTIONS IN ASIAN AND CAUCASIAN POPULATIONS

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Background: The gut microbiome plays a key role in metabolism and overall health, and its composition varies across populations and geographic regions. With growing interest in sustainable, plant-based protein sources, microalgae such as *Chlorella sorokiniana* are emerging as promising alternatives to animal-derived foods. Our study investigated the effects of *C. sorokiniana* consumption on the gut microbiome composition and metabolic profiles in healthy adults from diverse populations. **Methods:** Baseline microbiome profiling across a large cohort (n = 389) revealed significant compositional differences between Caucasian and Asian populations. Two parallel, randomized, double-blind, controlled intervention trials were conducted in German and Singaporean cohorts. In total, 176 participants consumed buns daily for two weeks containing either 0 g (control), 6 g, or 12 g of *C. sorokiniana*. Stool samples were collected before and after the intervention and analyzed using 16S rRNA gene sequencing. Additional clinical and physiological parameters, including blood markers, fecal calprotectin, stool characteristics, and dietary intake, were recorded. *Ex-vivo* gut chemostat models and biorthogonal non-canonical amino acid tagging (BONCAT) were used to further assess microbial responses to microalgae exposure. **Results:** In the German population, microalgae consumption did not result in significant overall shift in gut microbial composition or diversity. However, participants receiving 12 g of *C. sorokiniana* showed microbiome-associated changes reflected by increased fecal calprotectin levels during the intervention, which returned to baseline during follow-up. A similar pattern was observed for leukocytes, a systemic inflammatory marker. *Ex-vivo* chemostat experiments further support distinct microbial activity responses to algae supplementation. Notably, BONCAT-based analysis indicates that microalgae supplementation stimulates the activity of specific gut bacteria, suggesting functional responses that were not captured by compositional profiling alone. **Conclusion:** *C. sorokiniana* intake modulates the gut microbiome-associated host response in a dose-dependent manner. Higher doses induce more pronounced, yet temporary, inflammatory and microbial activity changes without causing sustained alterations in overall community structure. Further integration of metagenomic and metabolomic analyses will be essential to clarify the functional consequences of these effects.

THE GUT MICROBIOME IN GLIOBLASTOMA: A PROSPECTIVE CASE–CONTROL STUDY

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Glioblastoma (GBM) is the most common primary malignant brain tumor in adults and remains associated with a poor prognosis despite aggressive multimodal treatment. This study investigates potential differences in the gut microbiome and mycobiome composition between patients with newly diagnosed GBM and healthy control subjects.

We enrolled 23 patients with newly diagnosed GBM treated at the University Hospital of Würzburg and 23 healthy control subjects. Rectal swabs were collected from GBM patients prior to surgical resection. DNA was extracted and subjected to 16S rRNA gene and ITS amplicon sequencing to characterize the gut bacterial and fungal communities, respectively. Additionally, serum interleukin levels were measured, and glial cell markers were assessed in tumor tissue. Fluorescence *in situ* hybridization (FISH) was performed on GBM tissue sections using universal eukaryotic and fungal-specific probes to investigate the presence of fungal elements within the tumor microenvironment.

No significant differences in alpha diversity were observed between groups. GBM patients showed significantly higher abundances of *Methanobrevibacter*, *Negativibacillus*, and *Schaalia*, while, *Roseburia*, *Flintibacter*, *Bacteroides*, *Adlercreutzia*, *Anaerostipes*, *Faecalibacillus* and others were significantly reduced. Among fungi, Candida glabrata was significantly enriched in GBM patients. FISH analysis did not detect any microbial elements in GBM tissue sections. Serum IL-2 and IL-12 levels were elevated in GBM patients but did not reach statistical significance.

Our preliminary findings suggest that GBM patients harbor a distinct gut microbial and fungal signature characterized by a reduction of butyrate-producing bacteria and an enrichment of Candida glabrata. These results warrant further investigation into the role of the gut-brain axis in GBM pathogenesis and its potential as a therapeutic target.

INTRA-GASTROINTESTINAL MICROBIOME ORGANIZATION OF MICE ON HIGH-FAT OR HIGH-FIBER DIET

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Introduction: Studying the influence of different dietary conditions on the microbiome, most studies focus on the stool microbiome, disregarding potential variable effects at gastric, small and large intestinal locations within the gastrointestinal (GI) tract.

Materials and Methods: Over a four-week period, mice were assigned to a control, 15-hour fasting with control feed, high-fat, or high-fiber diet. Fecal samples were collected in the fourth intervention week, and GI segment samples (gastric, duodenum, jejunum, ileum, cecum, colon) were obtained post-euthanasia by phosphate-buffered saline flushing and centrifugation to obtain pellets with luminal content. Luminal content mass (g), bacterial density (16S rRNA gene copies/g luminal content), and total bacterial load (16S rRNA gene copies/luminal content) were determined, as well as taxonomic diversity and composition at the phylum and genus levels, using universal bacterial 16S rRNA gene quantitative PCR and amplicon sequencing.

Results and Discussion: Relative to the stomach, luminal content mass decreased in the small intestine (duodenum and jejunum). In contrast, bacterial density and total bacterial load, as well as taxonomic microbiota diversity (Shannon index), increased in the cecum and colon, consistent with disproportionate microbiome accumulation and/or proliferation in the stomach and lower GI tract. The ratio of Firmicutes to Bacteroidetes relative abundance flipped between upper and lower GI tract, with Firmicutes dominating gastric, duodenal, jejunal and ileal samples and Bacteroidetes cecum, colon and stool. Compared to the control diet, high-fiber diet increased the luminal content mass, but decreased bacterial density and total bacterial load throughout the entire GI tract, whereas high-fat diet decreased the luminal content and increased bacterial density and load, but only in the lower GI tract. Interestingly, taxonomic compositional differences between the upper and lower GI tract microbiota (Bray-Curtis dissimilarity) were more pronounced in high-fiber diet-fed mice, whereas high-fat diet reduced this compositional separation, mostly via increased relative abundance of Firmicutes in cecal, colonic and fecal samples.

Conclusion: Differential modulation of upper and lower GI tract microbiomes by high-fat and high-fiber diets suggests involvement of GI section-specific host-microbiome interactions in diet-dependent health and disease effects that should be further explored.

GLOBAL PATTERNS FROM 180,000 HUMAN GUT METAGENOMES

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The factors shaping human gut microbiome variation are a major focus of biomedical research. However, cross-study inference is limited by fragmented metagenomic data, inconsistent processing, and incomplete metadata. We assembled the MG180K, a global compendium of 181,032 human gut metagenomes from 507 studies and processed all data using a single standardized workflow to generate comparable taxonomic and functional profiles. We used MG180K to quantify biological, geographic, and technical drivers of microbiome variation and to test whether microbiome-based predictions generalize across studies. Using machine learning and a newly developed deep learning framework based on variational autoencoders (VAEs), we identified compact microbial signatures that robustly predict major diseases, including inflammatory bowel disease (IBD) and colorectal cancer (CRC), as well as geography and the Human Development Index (HDI). Our models explicitly control for confounding factors and support technically robust integration of future datasets. Finally, the VAE framework enabled the generation of realistic synthetic microbiome profiles from user-defined prompts. This work provides a new foundation for comparative metagenomics, with applications in cross-study microbiome prediction, data harmonization, and synthetic microbiome generation

ASSESSING INDIVIDUAL COLONISATION RESISTANCE USING HUMAN-GUT-DERIVED MICROBIAL COMMUNITIES

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The human gut microbiome performs various functions. Besides aiding digestion and producing vitamins, the microbiota can prevent the colonisation of pathogens via a process known as 'colonisation resistance'. This process includes mechanisms such as nutrient niche competition, bacteriocins, and defence mechanisms such as the type VI secretion system (T6SS), as well as the secretion of interfering metabolites. However, underlying diseases, diet, the host's genetic factors or medication can impair the effectiveness of this colonisation resistance, leading to increased pathogen colonisation in the gut and thereby enhancing the risk of difficult-to-treat infections.

We use native human stool samples, stabilized microbial communities from human stool samples (SMCs) and human stool sample-derived personalised microbial communities (PMCs) to evaluate variations in an individual's colonisation resistance *in vitro*. We performed 'Spike-in' assays of clinical isolates of different multi drug resistant Enterobacterales (MDR-E) into native human stool samples or community models (SMCs or PMCs) to investigate how different bacterial ecosystems affect initial colonisation and expansion of indicator strains. This approach aims to identify microbial consortia with high colonisation resistance, indicating strong protection against MDR-E colonisation, while also uncovering strain-specific differences in how these pathogens are inhibited. To further study the underlying processes, we complement this approach by compositional and functional analysis of the communities using 16S rRNA sequencing, shotgun metagenomics and metabolomics.

Notably, while recent studies have shed light on the mechanisms driving colonisation resistance, we still cannot predict an individual's risk of colonization by an MDR-E strain based on their microbiome composition. Understanding the underlying mechanisms may reveal predictive markers to distinguish communities with high or low colonisation resistance and thereby enable the assessment of the infection risk with MDR-E .

ORAL CARE IMPACT OF TWO PROBIOTIC STRAINS

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Background: Dental plaque-induced gingivitis is a highly prevalent, reversible inflammatory condition and represents an early stage of periodontal disease. Strategies that selectively modulate the oral microbiome and host inflammatory responses, such as oral probiotics, have gained increasing scientific interest. The PrOH-ACT study investigated whether two well-characterized probiotic strains, *Lactobacillus paracasei* LPc-G110 and *Lactobacillus plantarum* GOS42, enhance gingival health and oral ecosystem resilience during an experimental gingivitis challenge.
Methods: This triple-blind, randomized, placebo-controlled, parallel-group clinical trial enrolled 117 systemically healthy adults aged 18–55 years. Participants received lozenges containing *L. paracasei* LPc-G110, *L. plantarum* GOS42, or placebo three times daily for four weeks. The study design comprised a two-week wash-in period under normal oral hygiene conditions, a two-week experimental gingivitis phase with complete abstention from oral hygiene, and a two-week wash-out phase with reinstated oral hygiene. The primary endpoint was the change in bleeding on marginal probing (BOMP). Secondary endpoints included the Modified Gingival Index (MGI), plaque quantity and maturity, salivary inflammatory biomarkers, and microbiological parameters of the oral ecosystem.
Results: The primary endpoint, change in gingival bleeding following experimental gingivitis, did not differ significantly between treatment groups. In contrast, both probiotic interventions were associated with a significantly improved recovery of gingival health, as assessed by MGI, during the wash-out phase compared with placebo. Notably, administration of *L. paracasei* LPc-G110 was associated with reduced accumulation of mature dental plaque, lower salivary concentrations of the pro-inflammatory cytokine IL-1β, and more pronounced modulation of the oral microbiome, particularly at the tongue surface. Treatment compliance was high, and both probiotic formulations were well tolerated.
Conclusion: Although oral supplementation with *L. paracasei* LPc-G110 or *L. plantarum* GOS42 did not attenuate gingival bleeding during experimentally induced gingivitis, both strains supported post-challenge recovery of gingival health and demonstrated anti-inflammatory and microbiome-modulating effects. These findings indicate that selected oral probiotic strains may contribute to strengthening oral ecosystem resilience and represent a promising adjunctive approach for the maintenance of gingival health.

ION-DEPENDENT PHAGE DECOLONIZATION OF VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM* (VRE) IN AN *IN VITRO* GUT MODEL

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Enterococcus faecium is a natural member of the human gut microbiome but also part of the infamous group of ESKAPE pathogens. Under healthy conditions, this pathobiont exhibits low virulence and is usually harmless. However, diseases that alter immune function or trigger dysbiosis can promote *E. faecium* overgrowth, leading to severe infections such as sepsis and endocarditis [5]. In particular, vancomycin-resistant *Enterococcus* (VRE) strains, classified by the WHO as “high-priority” pathogens [6], represent a major cause of nosocomial infections, especially among immunocompromised patients. Oncology patients are particularly affected due to chemotherapy-induced gut damage and microbial dysbiosis, which facilitates VRE colonization [7]. In general, VRE infections are difficult to treat, and linezolid remains the only effective antibiotic, an expensive reserve antibiotic with serious side effects [8]. Therefore, alternative treatment strategies for VRE are urgently needed. As part of the DZIF Flagship project EVREA-phage, we evaluated the efficacy of a four-bacteriophage cocktail designed for preventive VRE decolonization. Using anoxic growth kinetic assays and a bioreactor-based *in vitro* gut community model (*iv*GCM), we evaluated its activity under colon-like conditions, which can alter phage performance through metabolic and receptor-related changes [9]. We could demonstrate that under these conditions, the phages strictly required divalent cations (Mg^{2+} and Ca^{2+}) for effective VRE lysis in monoculture and within a representative gut microbiota. Overall, we were able to reduce VRE colonization within the ivGCM by 2.5-log steps with a single dose of the phage cocktail and divalent ion supplementation. The results deliver important preclinical data relevant for future formulations of a suitable phage product based on the selected bacteriophages. By demonstrating that the efficacy of the selected phages depends critically on the availability of divalent ions, we identified both a promising therapeutic candidate and an important ecological factor that influences the outcome of the treatment.

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A WIDESPREAD SCC*MEC*-LOCATED GENE CLUSTER PROTECTS MRSA AGAINST TOXIC POLYSULFIDES

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Colonization of the human body presents challenges for pathobionts, which must overcome host defense mechanisms, antimicrobial compounds, and competition with the commensal microbiota. One of these pathobionts is *Staphylococcus aureus* (*S. aureus*), with methicillin-resistant *S. aureus* (MRSA) being among the most common antibiotic-resistant nosocomial pathogens, responsible for millions of life-threatening infections worldwide[8]. *S. aureus* often colonizes mucosal surfaces of the human body and is therefore exposed to environmental stressors, including hydrogen sulfide (H_2S). H_2S is ubiquitous in the human body, and while low concentrations act in regulatory signaling, high concentrations are toxic. These elevated H_2S levels are primarily derived from bacterial metabolization of sulfur compounds within the human microbiome. On mucosal surfaces, such as the nose and gut, H_2S concentrations can reach up to 0.4 mM[9] and 3.4 mM[10,11], respectively, due to the degradation of sulfated sugar residues and L-cysteine from mucin[12]. Under oxic conditions, which prevail on mucosal surfaces and which are potentiated under dysbiosis[13], H_2S oxidizes into highly reactive polysulfides, creating another toxic stressor for the bacteria. While it is known that *S. aureus* protects itself from H_2S via its *cst* gene cluster (*tauE, cstR, cstA, cstB, sqr*)[14], the detoxification of polysulfides is virtually unknown. Our results show that *S. aureus* uses an SQR-independent variant of the *cst* pathway to detoxify polysulfides. Furthermore, we found that the *cst* gene cluster is heterogeneously distributed in staphylococcal genomes, with multiple SCC*mec* types introducing an additional *cst* (*cst2*, without *sqr*) into the genomes of MRSA strains. Phenotypic analyses of a wide range of strains demonstrated that the additional *cst2* confers high polysulfide tolerance to MRSA, providing a significant fitness advantage in polysulfide-rich environments that results in the displacement of MSSA strains in direct intraspecies competition even in the absence of β-lactams.

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MICROBIAL STRAIN PERSISTENCE ALONG THE HUMAN GASTROINTESTINAL TRACT

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The oral and upper gastrointestinal (GI) microbiomes are increasingly recognized as critical contributors to local and systemic health and disease. However, the relationship between oral, gastric and duodenal microbiota remains understudied, as previous studies mostly focused only on a single location. To quantify and characterize microbiome overlap along the GI tract at the species and strain level, metagenomic sequencing of saliva, gastric flush, duodenal flush, and stool samples from the same individuals (n ≥ 17) was carried out. Taxonomic profiling was performed using MetaPhlAn and strain-level analysis with SameStr. Functional traits of detected species were annotated using MetaTraits to investigate associations with species and strain GI persistence. Species that were detected in saliva also accounted for the vast majority of species (87-89%) and total microbiota (97% relative abundance) in the stomach and duodenum and still represented 9% of all species and 5% of the total relative abundance in stool samples. At the strain level, 27% of stomach species were represented by a shared strain (63% relative abundance) and 16% by a distinct (13% relative abundance) relative to saliva, with a comparable pattern observed in the duodenum with 26% of species represented by shared (70% relative abundance) and 16% by distinct strains (16% relative abundance). These findings identify salivary strains as the predominant contributors to microbial abundance across the upper gastrointestinal tract. On the taxonomic level, considerable variations in strain persistence along the GI tract were observed, with the ratio of identical to distinct strains decreasing from *Prevotellaceae* (0.71) to *Veillonellaceae* (0.68), *Actinomycetaceae* (0.66), *Streptococcaceae* (0.43), and *Lachnospiraceae* species (0.37). Notably, strain sharing between saliva and duodenum was more frequent in species with lower pH growth requirements, based on MetaTraits annotations, suggesting that passage through the low-pH gastric environment represents a bottleneck for the persistence of salivary strains in the intestine. In contrast, a higher intra-species nucleotide diversity, as annotated by MetaTraits, was associated with a reduced frequency of shared strain detections in saliva and duodenum, suggesting distinct intra-individual subspecies populations. These findings demonstrate direct, major contributions of oral strains to the small intestinal microbiome through passive strain transmission. For other, minor taxa, they suggest oral and small intestinal location-specific intra-individual strain variations and potential adaptations that should be further studied.

FROM FAIR INFRASTRUCTURE TO DISCOVERY: NFDI4MICROBIOTA ENABLES PLANETARY-SCALE RESEARCH

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Modern microbiome research increasingly depends on the integration of massive, heterogeneous datasets spanning ecosystems and hosts. However, disconnected resources, inconsistent metadata standards, and inaccessible computational infrastructure continue to limit the reuse and integration of microbiome data. NFDI4Microbiota develops FAIR, interoperable, and community-driven infrastructures that connect microbiome data, metadata, analytics, and biological knowledge into an integrated research ecosystem. Central to this effort are resources such as metaTraits, a large-scale microbial trait database integrating experimentally derived and genome-predicted phenotypes across >2 million genomes and MAGs, and Metalog, a repository for harmonized contextual metadata. Together with EMBL's proGenomes and SPIRE databases, they standardize and enrich microbiomes with ecological, physiological, and taxonomic context. This integrated infrastructure enabled our recent planetary-scale microbiome study published in *Cell*, which analyzed >85,000 metagenomes across global ecosystems to delineate 40 microbial habitat clusters and investigate microbial dispersal and horizontal gene transfer. By combining uniformly processed metagenomes from SPIRE with context from Metalog and metaTraits annotations, the study revealed that a small subset of highly adaptable microbial generalists mediates gene flow across ecologically disparate habitats, including the dissemination of antimicrobial resistance genes between host-associated, anthropogenic, and environmental microbiomes. Anthropogenic interfaces such as wastewater accelerate this connectivity, underscoring the relevance of the One Health concept. Importantly, NFDI4Microbiota's Cloud-based Workflow Manager (CloWM) openly hosts the underlying workflows, alongside many other curated community pipelines, including those from nf-core. CloWM provides scalable workflow execution via a web-based interface and API, democratizing access to high-performance analytics and enabling the wider community to reproduce and reapply such large-scale analyses. NFDI4Microbiota thus transforms fragmented microbiome resources into FAIR infrastructure that enables high-impact biological discovery and reproducible planetary-scale microbiome research.

MULTIPLEXED PROTEIN-COMPOUND INTERACTION SCREEN UNRAVELS AN UNCONVENTIONAL CRP REGULATOR IN BACTEROIDES

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The gut microbiome is a complex integral part of human physiology and has long been known to play an essential role in human health and disease. Protein functional annotation in gut microbiome species is incomplete, with information about protein existence, let alone function, being mainly based on predictions. A systematic understanding of protein function in these bacteria will not only provide insights into their basic cellular processes but it will also contribute to better understanding of the formation, interplay and molecular function of the microbiome in relation to the host. Here, we developed a multiplexed Thermal Proteome Profiling-based approach to systematically assign protein function using protein-compound interactions as proxy. This involved treatment of crude lysates with pools of different compounds, allowing increase of throughput while ensuring deconvolution. We screened lysates of *P.vulgatus* and *B.uniformis* with 56 compounds covering different aspects of bacterial physiology, from nutrients to antibiotics, probing approximately 200 thousand potential protein-compound interactions. We identified an unconventional CRP regulator that directly and specifically binds non-phosphorylated glucose – which in turn promotes its association with DNA – and allows these bacteria to utilize oligosaccharides that contain at least one glucose molecule. The residues coordinating glucose are conserved within Bacteroidales, suggesting that this regulation might be absent from other gut bacteria. We propose that Bacteroides cells use this regulation to read the glucose content of more complex sugars and prioritize their metabolism accordingly, and that this offers them a unique niche within the complex communities of the gut.

EARLY CHILDHOOD HIGH ABUNDANCE OF GUT BACTEROIDES IS ASSOCIATED WITH INCREASED RISK FOR DEVELOPING EAR NOSE AND THROAT INFECTIONS AND CONTRIBUTES TO A HIGH DEGREE OF MICROBIOTA STABILITY AND RESILIENCE AFTER DYSBIOTIC EVENTS

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We investigated whether specific bacterial taxa in early childhood

1.) predispose to the development of childhood infections, and

2.) influence the microbiota stability and resilience after dysbiotic events.

Therefore, we explored 16S rRNA-sequencing data of stool samples from children in the German LöwenKIDS birth cohort study. The cohort includes 782 children, which were followed up since birth using , symptom-diaries, stool- and nasal swap-sampling. The subcohort contained 285 children of which 162 provided regular stool samples approx. every 3 months in the first two years of their lives. 49 children received a total of 66 antibiotic treatment episodes, mainly comprising Aminopenicillins (36%) and Cephalosporins (48%). Causes of antibiotic treatment were mainly ear nose throat (ENT) infections (73%) and urogenital infections (7.6%). 113 children did not receive antibiotics in this timeframe. Dysbiotic events were defined as episodes of antibiotic treatment, which followed either real or suspected infections, or were prescribed prophylactically. As expected, alpha-diversity steadily increased with age, and the community composition changed from a mainly Bifidobacteria-driven to a more complex composition that still contained high levels of Bifidobacteria, but also high levels of Firmicutes and Bacteroidetes. The average beta-diversities between individuals decreased with age.

We compared community compositions between the dysbiotic event group vs. control group in four intervals before and after dysbiotic events, which are long-term pre (45 - 225 days pretreatment), immediate pre (0 – 30 days pretreatment), immediate post (0-30 days post treatment), and long-term post (>90 days post treatment and >540 days of age). To account for community differences by age, we compared cumulative probabilities of the empirical distribution within age-matched samples of the control group. This approach revealed that ENT infections were associated with increased abundances of genus Bacteroides before treatment (long-term and immediate). Collinsella was

decreased in the immediate post treatment phase. Blautia was increased in the long-term post treatment phase. Interestingly, low Bacteroides levels correlated with decreased Shannon diversity following disease + antibiotic treatment, while high Bacteroides levels were associated with high microbiota stability and resilience. To verify the results with an independent analysis strategy, we applied zero inflated negative binomial mixed models with individuals as random variable. This approach confirmed that increased Bacteroides were associated with development of ENT infections. We currently analyze whether this model also confirms the role of Bacteroides for microbiota stability and resilience after dysbiotic events.

MAPPING CELL-SURFACE PROTEIN COMPLEXES IN BACTEROIDALES

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Bacteroidota represent the most abundant gram-negative bacterial phylum in the human gut, yet much of their biology remains understudied. Given the central role of the outer membrane in bacterial survival and as a platform for cell-surface molecules that mediate interactions with other species and the host, we are investigating the surface proteomes of the Bacteroidota model organisms *Phocaeicola vulgatus* and *Bacteroides uniformis*. To systematically identify surface-exposed membrane proteins, define their functional and physical interactions, and determine how they are translocated to the cell surface, we are combining bacterial genetics with subcellular fractionation and quantitative proteomics. Specifically, inner and outer membrane proteins are localised using sucrose density gradient fractionation and differential detergent solubility coupled to LC–MS/MS. To map cell-surface protein topology, we are further developing and optimising a sensitive workflow where we shave whole cells with exogenous proteases, and analyse the resulting peptide mixture with LC-MS/MS. Finally, to elucidate mechanisms of protein trafficking, we are testing candidate translocase proteins for defects in cell-surface localisation.

UNRAVELING THE ARSENAL AND MECHANISMS THAT BACTEROIDETES USE FOR KIN COMPETITION

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We have traditionally studied microbial physiology and functions in a reductionist way – growing microbes in isolation under well-controlled conditions. Unsurprisingly, functions relevant for interactions with other microbes, predators (e.g. phages) or hosts have remained understudied. Such functions are of particular interest for human gut microbes, which live as part of complex stable communities in dynamic environments. In these communities, phylogenetically similar species and strains often compete for the same niche, using various toxic modalities to attack each other, as shown previously for model enterobacteria. In recent years, both broad-spectrum and narrow-spectrum toxins have been identified in prevalent and abundant species of the human gut microbiota, particularly among members of the Bacteroidota phylum. Such antimicrobials are likely integral for the stability, individuality and colonization resistance of the human gut microbiome.

Here, we have systematically screened a large strain collection of *Phocaeicola vulgatus* isolates for antagonistic activity and uncovered extensive intraspecies inhibition mediated by narrow-spectrum secreted toxins. We then generated and arrayed transposon insertion mutant libraries in different toxin-producing strains and used our high-throughput interaction assays to identify the underlying toxin-producing genetic loci, leading to the discovery of two novel bacteriocin-immunity gene pairs at their core. The toxin-immunity pairs are encoded within biosynthetic gene clusters, which we further characterized through genetic deletion and complementation experiments. Notably, these bacteriocins displayed highly specific killing restricted to closely related *P. vulgatus* strains and we therefore named them Vulgatocin A and B. Transfer of the Vulgatocin A gene cluster into another *P. vulgatus* strain was sufficient to allow the recipient strain to displace its parental sensitive counterparts *in vitro* and *in vivo* in mice.

Collectively, these findings indicate that we have discovered two new bacteriocin classes from one of the most prevalent and abundant gut bacterial species. The complex genetic architecture of the biosynthetic gene clusters and the involvement of various other core genes outside of these clusters, hints towards unknown mechanisms behind bacteriocin biosynthesis and deployment in *P. vulgatus*.

FOR GUT'S SAKE – NFDI4MICROBIOTA FACILITATES SUSTAINABLE MICROBIOME RESEARCH

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NFDI4Microbiota supports researchers in conducting sustainable microbiome research, covering a rich tasks portfolio from standardized data generation and metadata annotation to scalable analysis workflows and the reuse of data and software. While many best-practice approaches have already been established, including for gut-specific analyses, several challenges still remain.

Standardized data generation and metadata annotation

For gut microbiome studies, biomarker sequencing data (e.g., 16S, 18S, ITS) can be analyzed using the Qiita instance hosted in Germany. The use of community-approved EMPO and MIxS metadata templates enables a consistent description of host-associated and body-site-specific metadata.

Scalable computational analysis infrastructure

NFDI4Microbiota provides CloWM, a web-based workflow platform with pre-installed, community-established pipelines for amplicon and shotgun sequencing analysis, transcriptomics, genome assembly, phylogenomics, and infectious disease genomics. Additional nf-core- and Nextflow-compatible workflows can be contributed by researchers, while the CAMI benchmarking portal supports the validation of metagenomic computational methods. Data can be stored in ARUNA and processed directly through CloWM, reducing transfer barriers and enabling scalable analyses.

Collection of specialized resources

metaTraits supports the functional interpretation of cultured bacteria by compiling information on metabolic functions and environmental preferences. For viral components across different hosts, VirJenDB provides curated viral datasets and standardized metadata templates. Protologger enables the consistent description of novel taxa, while StrainInfo and StrainRegistry ensure the assignment of persistent strain identifiers and improve the traceability of newly described strains.

Community involvement

Despite NFDI4Microbiota's efforts to support FAIR microbiome research, challenges remain to establish open and efficient deposition strategies for microbiome data. In this context, please let us know what you need!

ESTABLISHMENT OF A QUANTITATIVE SCREENING PLATFORM FOR FIBER DEGRADATION BY GUT

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The gut microbiota plays a critical role in human health by fermenting dietary fibres into beneficial metabolites, including short-chain fatty acids (SCFAs). However, interactions between gut microbes and fibre are complex and poorly understood. While diet-driven variations in microbiota community composition have been well studied, bulk approaches such as faecal sampling and metagenomics obscure critical insights into the spatial and ecological context of these processes. To understand how gut commensals partition into nutritional niches and to resolve ecological interaction networks shaped by dietary substrates, we need nondisruptive experimental approaches that can capture small-scale interactions over time. Here, we refine a bead-based spatial ecology platform that has been deployed to study interactions between dietary fibres and gut strain isolates. Our results reveal strain-specific binding profiles to different dietary substrates, which were primarily driven by the nutritional background and succession time.

The presented bead-based platform's capacity to multiplex fiber substrate tests, combined with our added capacity to identify multiple strains will provide a valuable basis for scalable, community experiments on the ecology of fiber degradation and targeted microbiome-based therapies

NEXT-GENERATION SEQUENCING FOR DETECTION OF ASCITIC FUNGAL INFECTIONS IN SURGICAL ICU PATIENTS

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Objectives:

Fungal infection of ascitic fluid is a severe complication in critically ill patients and is associated with increased morbidity and mortality, particularly in intensive care settings. Conventional culture-based diagnostics often lack sensitivity and may fail to detect relevant fungal pathogens. This study assessed the utility of next-generation sequencing (NGS) for molecular detection and characterization of fungal species in ascitic fluid samples from surgical ICU patients.

Methods:

In this prospective pilot study, 50 ascitic fluid samples were collected from ICU patients with suspected ascites infection. All samples underwent routine microbiological culture. In parallel, aliquots were processed for fungal DNA extraction, followed by ITS2 PCR amplification and NGS-based fungal species identification.

Results:

Candida spp. were detected by conventional culture in 5 of 50 samples. Following DNA extraction and ITS2 PCR, successful amplification was achieved in 10 samples. NGS identified facultative pathogenic fungi in 19 patients. In 15 cases, sequencing revealed additional potentially relevant fungal organisms not detected by culture alone. Detection of fungal DNA by NGS was significantly associated with adverse clinical outcome and several clinical risk parameters.

Conclusions:

NGS-based fungal diagnostics demonstrated higher sensitivity than standard culture for detecting fungal pathogens in ascitic fluid. These findings suggest that molecular sequencing may improve diagnostic resolution in critically ill patients with suspected fungal ascitic infection and support more targeted antifungal treatment. Clinical implementation will require workflow standardization and careful interpretation of sequencing results in the clinical context.

OCCURRENCE AND CHARACTERIZATION OF TYPE VI SECRETION SYSTEM GENES IN THE HUMAN GUT

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Bacteroidota is one of the most abundant phyla of the human gut microbiome, where their population dynamics profoundly impact host health and resistance to diseases and infections. Gram-negative gut residents of the *Bacteroidota* deploy the subtype iii Type VI Secretion System (T6SSiii) alongside unique effector and immunity proteins to mediate interbacterial competition. Despite its potential role in microbial community structure, the specific impact of the T6SSiii on gut microbiome stability remains little characterized because of limited knowledge on the presence and absence of the T6SSs and the large number of unidentified effector proteins. To address this, we utilized targeted bioinformatic pipelines, including MacSyFinder, to identify functional sets of T6SS genes in publicly available sequenced *Bacteroidota* genomes. We found genomes of multiple species with T6SS genes, including members of synthetic gut microbial communities. Functional testing revealed toxicity of putative effectors with unknown function. Understanding T6SS-mediated interactions might contribute to the development of strategies to enhance microbiome resilience against pathogenic invasion and improve treatments for dysbiosis-related illnesses

DETERMINATION OF OXYGEN CONSUMPTIONS RATES IN *SEGATELLA COPRI* DSM 18205 USING OPTICAL OXYGEN SENSORS

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Segatella copri is a key resident of the human microbiome. Depending on the strain, positive associations with improved host metabolism, food allergies and glucose homeostasis were observed. These observations led to the suggestion that specific strains of *Segatella copri* could be the next generation probiotic. However, the strict anaerobic requirements of *Segatella copri* limit the application as a probiotic in a patient- friendly manner, since exposure to air (21% O_2) is detrimental for viability [1]. As low concentrations of oxygen (0-30 Torr) are found in differents parts of the human gut, we propose that *S. copri* possesses mechanisms that enable it to tolerate such levels of oxygen.

Quite unexpectedly, a genome analysis of *S. copri* DSM 18205 revealed an absence of catalase and superoxide dismutase, enzymes which typically counteract oxidative stress. However, *S. copri* DSM 18205 harbors genes encoding a terminal oxidase of the bd- type (quinol oxidase) and a thioredoxin-dependent reduction system. The activity of these enzymatic systems might provide protection against oxidative stress. To test this hypothesis, we established a method to determine the specific oxygen consumption rate (OCR) of *S. copri* cells via optical oxygen sensors. The method was validated using *E. coli* K12 cells. *E. coli* exhibited OCR of 40 nmol O_2 min^{-1} mg^{-1} which compares favorably with previously reported rates [2]. *S. copri* was grown in Schaedler broth (DSMZ 1669) medium with 1,5g/L cystein- HCl. Cells from the stationary phase were harvested by centrifugation, and the pellet was resuspended in anaerobic medium which was also used for the determination of OCR. Addition of air-saturated medium was followed by immediate oxygen consumption by *S. copri*. In comparison with washed *E. coli* cells, *S. copri* showed OCRs of ca. 2 – 10 % of the rates observed with *E. coli*. This suggests that *S. copri* DSM 18205 is capable to convert O_2 in a reductive process which might protect the cells from the detrimental effects of O_2.

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REDEFINING MICROBIAL CONTRIBUTIONS TO NITROGEN METABOLISM IN UREA CYCLE DISORDERS

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Urea cycle disorders are inherited defects in nitrogen detoxification that can lead to impaired ammonia clearance and metabolic instability. Although the gut microbiota is widely considered an important contributor to systemic nitrogen load, its functional role in urea cycle disorders remains incompletely understood. In particular, it remains unclear whether intestinal microbes primarily aggravate host nitrogen stress through ammonia production or whether they participate in broader nitrogen redistribution across host and microbial compartments.

To address this question, we combined targeted metabolomics, gnotobiotic mouse models, metagenomics, and host transcriptomics to investigate host-microbiota interactions in nitrogen metabolism. We first developed a liquid chromatography-high-resolution mass spectrometry workflow for the quantitative analysis of reduced nitrogen metabolites. This method enabled us to simultaneously identify fifty biologically relevant nitrogen-containing compounds, including ammonia, amino acids, polyamines, neurotransmitters, nucleobases, catecholamines, urea cycle intermediates, and related metabolites across biological matrices.

We applied this analytical framework to the *SpfAsh* mouse model of ornithine transcarbamylase deficiency, comparing germ-free and specific pathogen-free conditions. Contrary to the prevailing assumption that microbial colonisation necessarily increases systemic ammonia burden, colonised OTC-deficient mice did not show worsened systemic ammonia concentrations or physiological

outcomes, despite increased luminal ammonia levels. Instead, germ-free OTC-deficient mice were more vulnerable to dietary protein challenge, while microbial colonisation substantially reshaped intestinal amino acid pools. These findings suggest that the microbiota contributes to nitrogen handling through assimilation and redistribution of nitrogen substrates rather than through ammonia production alone.

Shotgun metagenomic analysis further revealed that impaired host nitrogen metabolism was associated with reproducible shifts in microbial functional potential. While overall community diversity remained largely stable, OTC deficiency was linked to genotype-dependent differences in pathways related to carbohydrate uptake and amino acid metabolism. Notably, OTC-deficient mice showed depletion of *Dubosiella newyorkensis* and reduced abundance of AspC-family aminotransferases, indicating altered microbial amino acid transformation capacity. In contrast, genes associated with urease activity were not increased, challenging the idea that enhanced microbial ureolysis is a dominant driver of nitrogen imbalance in this model.

Together, these results redefine the gut microbiota as a dynamic nitrogen-processing compartment in urea cycle disorders. Rather than acting solely as a source of ammonia, microbial communities appear to modulate host nitrogen metabolism by transforming, assimilating, and redistributing nitrogen substrates. This work provides a systems-level framework for understanding nitrogen partitioning across host and microbial metabolism and highlights the importance of integrated host-microbiota approaches in clinically relevant disorders of nitrogen detoxification.

BACTEROIDES-MEDIATED GLYCAN PROCESSING SHAPES NUTRIENT AVAILABILITY FOR AN ENTERIC PATHOGEN

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While the microbial community protects our intestine from invaders, commensal microbes can also generate metabolic niches that promote pathogen expansion. For example, glycan degradation by the dominant gut bacterial genus *Bacteroides* releases metabolites that can be exploited by enteropathogens such as *Salmonella enterica* serovar Typhimurium (*S.* Tm). Here, we dissect the mechanisms and relevance of cross-feeding from the model organism *Bacteroides thetaiotaomicron* (*B. theta*) to *S.* Tm. Through metabolic profiling, we mapped metabolites released by *B. theta* during growth on distinct *in vivo*-relevant polysaccharides and identified those consumed by *S.* Tm. Targeted manipulation of Polysaccharide Utilization Loci (PULs) in *B. theta* revealed PUL genes required for cross-feeding, as well as genes whose modulation allowed for fine-tuning of metabolite availability *in vitro*. Using a gnotobiotic mouse model, we further confirmed that PUL-mediated glycan degradation by *B. theta* modulates *S.* Tm colonization *in vivo*. Mechanistically, we uncovered that outer membrane vesicles (OMVs) shape commensal-pathogen cross-feeding. OMVs released by *B. theta* in response to defined polysaccharides were substrate-specific and sufficient to enable *S.* Tm growth when supplemented into polysaccharide-containing media that otherwise does not sustain *S*. Tm growth. Functional disruption as well as overexpression of a PUL-encoded outer membrane hydrolase, preferentially packed into OMVs, altered the ability of OMVs to promote *S.* Tm utilization of specific polysaccharides. Together, these findings highlight vesicle-mediated glycan degradation as major contributor to microbial cross-feeding and demonstrate how carbon liberation by *B. theta* can promote *S.* Tm expansion.

INVESTIGATING THE INFLUENCE OF CONTEXT-DEPENDENT INTERACTIONS ON THE METAPROTEOMIC PROFILE OF A DEFINED GUT BACTERIAL COMMUNITY

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Bacterial interactions within the mammalian gastrointestinal tract are highly context-dependent and spatial variations along the gastrointestinal tract in oxygen levels, nutrient availability, as well as composition and thickness of the mucus layer influence the adaptation, physiological properties, and functional role of each bacterium within the gut microbiome. Synthetic communities such as OMM[12] allow us to study this complex, context-dependent ecosystem in a simplified yet representative way. OMM[12] is a model system comprising 12 bacterial species that reflect important characteristics and biological features of the murine gut microbiota. It has previously been shown that the absence of single members of this defined community (drop-out community) can have profound effects on community composition, function and colonisation resistance against pathogens. Here, we use metaproteomic analysis to investigate the community's functional adaptation to different spatial environments and altered microbial environments using drop-out communities as well as consortia of lower diversity.

We will generate species-resolved metaproteomic profiles from drop-out communities to identify differences relative to the full community, with a focus on context-dependent protein expression and the keystone roles of individual bacterial members. In parallel, we will assess how variations in culture medium composition and nutrient availability influence protein expression, thereby shaping community function and metabolic interactions. To better mimic the spatially structured nutrient landscape of the gut in vitro, we will also develop a system incorporating nutrient-infused beads into both batch and continuous culture setups. The beads, containing specific nutrients, enable bacteria that utilize these nutrients to preferentially colonise their surfaces.

The datasets will serve as a starting point for experiments aimed at investigating the complex context-dependent interaction network of the gut microbiome, providing mechanistic insights into its function, metabolism, and spatially distinct expression patterns.

DEVELOPMENT OF AN EX VIVO ASSAY TO CHARACTERIZE THE COLONIZATION RESISTANCE OF HUMAN STOOL SAMPLES AGAINST ENTERIC PATHOGENS

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The gut microbiome, a highly diverse and dynamic microbial community, plays a central role in human health. Among its key functions, colonization resistance (CR) describes the capacity of the resident microbiome to prevent invading pathogens from establishing and proliferating within the intestinal environment. CR emerges from complex interactions among commensal bacteria, the intestinal nutrient environment, and the host, giving rise to inter- and intraindividual differences in resistance to infection that remain incompletely understood. Characterizing the factors underlying this variation is therefore essential for identifying individuals at heightened risk of infection and for developing targeted preventive interventions.

To capture this variability, this project aims to establish an ex vivo assay specifically designed to measure the ability of sterile stool filtrates to inhibit or allow the growth of invading commensal and pathogenic Enterobacteriaceae, including Escherichia coli and Salmonella enterica serovar Typhimurium. This assay allows to directly assess the nutrient-driven mechanisms of CR while eliminating the effects of direct inhibitory mechanisms. For the assay development, stool samples were collected from 12 healthy adult volunteers over approximately one year, processed under anaerobic conditions, and filtered to obtain sterile stool filtrates. Test strains were subsequently spiked into sterile stool filtrates, and growth was monitored.

Preliminary results reveal donor-dependent differences in growth of invading Enterobacteriaceae, validating the assay's sensitivity to inter-individual variation in CR. Future proteomic profiling of pathogens recovered from high- and low-CR stool filtrates aims to map the nutrient utilization strategies underlying this variability, with the broader goal of identifying metabolic signatures that predict susceptibility to enteric infection.

ASSESSMENT OF THE SAFETY AND ACID STRESS RESISTANCE OF LACTIC ACID BACTERIA FROM THE BREAST MILK AND THE NEONATAL GUT MICROBIOME

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Lactic acid bacteria (LAB) are key members of the early-life microbiome, colonizing both human breast milk and the gastrointestinal tract of newborns. There, they contribute to host-microbe interactions and microbial homeostasis. Human-derived LAB, particularly members of the *Lactobacillus sensu lato* group (including *Lacticaseibacillus, Limosilactobacillus,* and *Lactiplantibacillus),* represent promising candidates for industrial and probiotic applications due to their capacity to withstand dynamic environmental stressors. However, their safe application requires a systematic evaluation of both safety-related traits and stress tolerance.

In this study, a total of 22 LAB strains were isolated from paired breast milk and fecal samples obtained from Bulgarian mother-infant dyads. These strains enable a comparative perspective on early microbial transmission and adaptation. MALDI-TOF MS was used for species identification, revealing a predominance of *Lacticaseibacillus rhamnosus* (n=15)*, Limosilactobacillus fermentum* (n=7), *Lacticaseibacillus paracasei* (n=4)*, Lactobacillus gasseri* (n=2)*,* and *Limosilactobacillus reuteri* (n=1).

A comprehensive safety screening demonstrated that the majority of isolates were susceptible to clinically relevant antibiotics (according to established criteria), with no indications of acquired resistance. All strains displayed a γ-hemolytic profile but did not exhibit DNase, lipase, or gelatinase activities. These findings support their favorable safety profile.

Acid stress tolerance, assessed as a model of gastrointestinal stress, revealed that a substantial proportion of isolates retained viability at low pH values. Notably, pronounced strain-specific variability was observed, with *L. rhamnosus, L. fermentum* and *L. reuteri.* They exhibited the highest levels of acid resistance, consistent with their known capability to withstand acid stress.

Collectively, these findings identify human-derived LAB (from breast milk and neonatal gut) as safe and functionally robust candidates for probiotic application. The observed combination of safety and stress resilience provides a solid basis for further mechanistic and genomic investigations aimed at targeted strain selection.

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