15TH SEEON CONFERENCE

MICROBIOTA, PROBIOTICS AND HOST

MIKROBIOTA, PROBIOTIKA UND WIRT

JUNE 29TH - JULY 1ST 2023

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KLOSTER SEEON KULTUR & BILDUNGS ZENTRUM

15TH SEEON CONFERENCE

MICROBIOTA, PROBIOTICS AND HOST

MIKROBIOTA, PROBIOTIKA UND WIRT

June 29th - July 1st 2023

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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

NAVIGATING THE DIGITAL ABSTRACT BAND

In the agenda/ program (p.4-9): The titles of the talks hyperlink to the abstracts. The date in the abstract header hyperlinks to the corresponding day in the agenda/ program (p.4-9).

The poster titles in "Poster session overview"(p.10) lead to the poster abstracts of each presenter.
You can jump back to the poster overview by following the hyperlinked header "POSTER" on the upper left-hand corner of each abstract.

Dear Participants,

We warmly welcome you at the Seeon Monastery for the 15th Conference on Microbiota-Host interactions.
This meeting is annually organized by the German Society of Hygiene and Microbiology **(DGHM) section "Microbiota, Probiotics and Host"**. Since the first event in 2008, the "Seeon Conference" has become a forum to integrate various disciplines in basic and clinical sciences unified by the aim to understand the human microbiome and its role in health and disease. Past activities around this conference have substantially contributed to the creation of the **DFG-funded Priority Program "MICROBIOTA – a Microbial Ecosystem at the Edge between Immune Homeostasis and Inflammation"** (SPP 1656), which gathered >30 research groups between 2013-2019. Since then, microbiome research has continued to bloom in Germany: established in 2015, the **Collaborative Research Center CRC1182 "Metaorganisms"** in Kiel studies how resident microbes influence fitness of their plant and animal hosts to form a holobiont. In 2018, the **Cluster of Excellence CMFI - Controlling Microbes to Fight Infections** in Tübingen was funded to elucidate the mechanisms of interaction between beneficial and harmful bacteria to make them useful for targeted therapeutic interventions. Since 2019, **CRC1371 "Microbiome Signatures"** in Munich, which aims to determine the precise functional relevance of microbiome signatures in disease-specific contexts, and **CRC1382 "Gut-liver axis"** in Aachen, which dissects microbiome-derived mediators involved in organ-crosstalk, further expanded this fruitful research landscape around the microbiome. Researchers from these consortia all meet in Seeon to discuss latest advances in their field.
Seeon is a scientific event that particularly fosters participation by young scientists. Besides the conference, the **Seeon Summer School on "Microbiome in Health and Disease"** was launched in 2018, with the aim to create a sustainable platform to train and promote young scientists across various disciplines, including gastroenterology, nutritional medicine, immunology, infection research, microbial ecology, synthetic biology, animal science, and computational biology in the area of basic and applied microbiome research.
This year again, we have a fantastic line-up of speakers and selected talks. We are looking forward to fruitful discussions and good science; let's have a great time together in Seeon!

Prof. Thomas Clavel,
on behalf of the Steering Committee:
ProfIN Maria Vehreschild, University Hospital Frankfurt am Main, Germany
Prof. Till Strowig, Helmholtz Center for Infection Research, Braunschweig, Germany

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Thursday, 29th June 2023		
14:00	16:00	Registration & Coffee
16:00	16:15	Welcoming
16:15	17:00	**Keynote Lecture - Paul Wilmes: Systems Ecology of the Human Expobiome**
17:00	18:00	Session 1: Metabolism & microbial dynamics
18:15	19:45	Dinner
20:00	21:30	Poster Slam (2 minutes/ slides)
Friday, 30th June 2023		
9:00	9:45	**Keynote Lecture - Melanie Blokesch: Molecular secrets of pandemic Vibrio cholerae**
9:45	10:45	Session 2: Drugs & modulating the microbiome
10:45	11:15	Coffee break/ Poster at first glance
11:15	12:00	**Keynote Lecture - Eric Martens: Opposing roles of bacterial mucus erosion and metabolite production in inflammatory bowel disease**
12:00	13:30	Lunch
13:30	14:15	**Keynote Lecture - Julia Frunzke: Antiphage molecules produced by bacteria**
14:15	15:15	Session 3: Microbiome in disease
15:15	15:45	Coffee break
15:45	16:05	**Hot topic - Mathilde Poyet: Host-microbiome interactions in the context of recent human evolution**
16:05	16:25	**Hot topic - Francesca Ronchi: The effect of ketogenic diet on the host microbiota, immune and central nervous system**
16:25	16:45	**Hot topic - Joel Selkrig Systematic Mapping of Bacterial Cell Surfaces**
16:45	17:15	DGHM Fachgruppenmeeting for members
16:45	19:00	Poster session
19:00		Dinner
Saturday, 1st July 2023		
9:00	9:45	**Keynote Lecture - Gianluca Ianiro: Key determinants of FMT success**
9:45	10:45	Session 4: Techniques in microbiome research
10:45	11:15	Coffee break
11:15	12:15	Session 5: Microbe-host interactions
12:15	12:45	Awards & Farewell
13:00		Lunch to Go
13:15		Shuttle to airport and train station

THURSDAY, JUNE 29TH 2023

14:00 - 16:00 Registration & Coffee

16:00 - 16:15 WELCOMING

By Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*

16:50 – 17:00 KEYNOTE LECTURE

System Ecology of the Human Expobiome
Paul Wilmes, *Luxembourg Centre for Systems Biomedicine, Department of Life Sciences and Medicine, Faculty of Science, Technology and Medicine, Université du Luxembourg, Luxembourg*

Chaired by Joel Selkrig*, Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*

17:00 – 18:00 SESSION 1 - METABOLISM & MICROBIAL DYNAMICS

Evaluating the Effect of Candidate Prebiotics in the Human Gut Microbiota by Activity-Based Cell Sorting and Targeted Isolation
Hamid Rasoulimerhrabani, *Center for Microbiology and Environmental Systems Science, Department of Micjoelrobiology and Ecosystem Science, Division of Microbial Ecology, University of Vienna, Austria*

Blautia Pseudococcoides and *Enterocloster Clostridioformis* Confer Colonization Resistance Against Segmented Filamentous Bacteria
Silvia Bolsega, *Institute for Laboratory Animal Science and Central Animal Facility, Hannover Medical School, Germany*

Therapeutic Potential of Tradeoffs During Adaptation of *E. Coli* to the Inflamed Mouse Gut
Rahul Unni, *Max-Planck Institute for Evolutionary Biology, Plön, Germany*

Chaired by Joel Selkrig*, Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*

18:15 - 19:45 Dinner

20:00 - 21:30 POSTER SLAM (2 MIN/ 2 SLIDES)

Chaired by Maja Magel, *Functional Microbiome Research Group, Institute of Medical Microbiology, University Hospital of RWTH Aachen, Aachen, Germany*

FRIDAY, 30TH JUNE 2023

9:00 - 9:45 KEYNOTE LECTURE

Molecular secrets of 7th pandemic *Vibrio cholerae*

Melanie Blokesch, *Laboratory of Molecular Microbiology, Global Health Institute, School of Life Sciences, Swiss Federal Institute of Technology Lausanne (EPFL), Lausanne, Switzerland*

Chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*

9:45 - 10:45 SESSION 2: DRUGS & MODULATING THE MICROBIOME

Chronic Exposure to Antiseizure Drugs Impacts the Gut Microbiota Community and Function

Camille Dop, *Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, Domaine de Vilvert, Jouy-en-Josa, France*

Systematically Investigating the Interactions between the Gut Microbiome and Psychotropic Drugs

Lara Berg, *Institute of Medical Microbiology and Hygiene, University Hospital Tübingen and Interfaculty Institute of Microbiology and Infection Medicine, University of Tübingen, Germany*

Differential Impact of Antibiotic Regiments Drive on Microbiome Alterations and Emergence of Fungi

Lena Biehl, *Department I of Internal Medicine, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany*

Phage Induced Strain Replacement within Microbiomes

Marla Gaissmaier, *Max von Pettenkofer Institute, Department of Bacteriology, LMU Munich, Germany*

Chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*

10:45 - 11:15 Coffee break/ POSTER AT FIRST GLANCE

11:15 - 12:00 KEYNOTE LECTURE

Opposing Roles of Bacterial Mucus Erosion and Metabolite Production in Inflammatory Bowel Disease

Eric Martens, *Professor of Microbiology and Immunology, University of Michigan Medical School, Ann Arbor, Michigan, USA*

Chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*

12:00 - 13:30 Lunch

13:30 - 14:15 KEYNOTE LECTURE

Antiphage Molecules Produced by Bacteria
Julia Frunzke, *IBG-1 Biotechnology, Institute of Bio- and Geosciences, Forschungszentrum Jülich, Jülich, Germany*

Chaired by Bärbel Stecher-Letsch, *Microbiota & Infections, Max von Pettekofer-Institute, LMU Munich, Germany*

14:15 - 15:15 SESSION 3: MICROBIOME IN DISEASE

Breaking Down Inflammatory Bowel Disease: How Metabolic Modeling Sheds Light on the Gut-Microbiome Connection
Jan Taubenheim, *Research Group Medical System Biology, Institute of Experimental Medicine, University of Kiel*

Characterization of Tumor Microbiome Using Shotgun Metagenome and 16S rRNA Gene Sequencing
Arnelyn Doloiras-Laraño, *Translational Microbiome Sciences, Internal Medicine I, University Clinic Tuebingen, Tuebingen, Germany*

Processed Diets Shift the Intestinal Microbiome and Exacerbate Tumorigenesis in Murine Models of ATF6-Driven Colon Cancer
Miriam Ecker, *Chair of Nutrition and Immunology, ZIEL, Technische Universität München, Freising, Germany*

Chaired by Bärbel Stecher-Letsch, *Microbiota & Infections, Max von Pettekofer-Institute, LMU Munich, Germany*

15:15 - 15:45 Coffee break

15:45 - 16:05 HOT TOPIC

Host-Microbiome Interactions in the Context of Recent Human Evolution *(cancelled)*
Mathilde Poyet, *Institute of Experimental Medicine, University of Kiel, Germany & Massachusetts Institute of Technology, United States, Global Microbiome Conservancy*

Chaired by Maria Vehreschild, *Infectiology, Medical Clinic II, University Hospital Frankfurt, Germany*

16:05 - 16:25 HOT TOPIC

The Effect of Ketogenic Diet on the Host Microbiota, Immune and Central Nervous System
Francesca Ronchi, *Institute of Microbiology, Infectious Diseases and Immunology (I-MIDI), Charité - Universitaetsmedizin Berlin, Germany*

Chaired by Maria Vehreschild, *Infectiology, Medical Clinic II, University Hospital Frankfurt, Germany*

16:25 -16:45 HOT TOPIC

Systematic Mapping of Bacterial Cell Surfaces
Joel Selkrig, *Institute of Medical Microbiology, Host-Microbe Interactomics Group, University Hospital of Aachen, Germany*

Chaired by Maria Vehreschild, *Infectiology, Medical Clinic II, University Hospital Frankfurt, Germany*

16:45 - 17:15 DGHM FACHGRUPPENMEETING FOR MEMBERS

16:45 - 19:00 POSTER SESSION

19:00 - Dinner

SATURDAY, 1ST JULY 2023

9:00 - 9:45 KEYNOTE LECTURE

Key determinants of FMT success
Gianluca Ianiro, *Digestive Disease Center, Fondazione Policlinico Universitario Gemelli IRCCS & Università Cattolica del Sacro Cuore, Rome, Italy*

Chaired by Maria Vehreschild, *Infectiology, Medical Clinic II, University Hospital Frankfurt, Germany*

9:45 - 10:45 SESSION 4 - TECHNIQUES IN MICROBIOME RESEARCH

Spike-In Quantification Techniques for Improved Microbiome Sequencing: Short- and Long-Read Applications
Bernd Daller, *Institute of Medical Microbiology and Hygiene, University Regensburg, Germany*

Deriving and Evaluating Microbial Profiles Obtained across Diverse Sequencing Technologies
Selin Pekel, *Structural and Computational Biology Unit, European Molecular Biology Laboratory, 69117 Heidelberg, Germany*

Towards Real-Time Imaging of the Gut Microbiome
Eden Laing, *Department of Preclinical Imaging and Radiopharmacy, Werner Siemens Imaging Center, Eberhard Karls University, Tübingen, Germany*

Investigating the Mode of Action of Non-Antibiotic Drugs on Human Gut Microbes by Microscopy
Leonardo Boldt, *Interfaculty Institute of Microbiology and Infection Medicine, University of Tuebingen and Institute of Medical Microbiology and Hygiene, University Hospital Tuebingen, Germany*

Chaired by Maria Vehreschild, *Infectiology, Medical Clinic II, University Hospital Frankfurt, Germany*

10:45 - 11:15 Coffee break

11:15 - 12:15 SESSION 5 - MICROBE-HOST INTERACTIONS

Effect of Early Life Colonization by Flagellated Bacteria on Enteric Epithelial Cell Responses and Microbiome Establishment
Atscharah Panyot, *Functional Microbiome Research Group, Institute of Medical Microbiology, University Hospital of RWTH Aachen, Aachen, Germany*

T Cell Skewing in Relation to Intestinal Dysbiosis and Graft-Versus-Host Disease in Allogeneic Stem Cell Transplantation
Sabrina Wagner, *Institute for Medical Microbiology, Immunology and Hygiene, Technical University of Munich (TUM), Munich, Germany*

Helicobacter Pylori Promotes Colorectal Carcinogenesis by Deregulating Intestinal Immunity and Inducing a Mucus-Degrading Microbiota Signature
Veronika Engelsberger, *Institute for Medical Microbiology, Immunology and Hygiene, School of Medicine, Technical University of Munich, Germany*

Chaired by Maria Vehreschild, *Infectiology, Medical Clinic II, University Hospital Frankfurt, Germany*

12:15 - 12:45 AWARDS & FAREWELL

Chaired by Maria Vehreschild, *Infectiology, Medical Clinic II, University Hospital Frankfurt, Germany*

and chaired by Till Strowig, *Microbial Immune Regulation, Helmholtz Centre for Infection Research, Braunschweig, Germany*

13:00 Lunch to Go

13:15 SHUTTLE TO AIRPORT AND TRAIN STATION

POSTER SESSION OVERVIEW

#1	Cacace	NITROGEN CYCLING IN THE HUMAN GUT MICROBIOME ACROSS AGES OF LIFE
#2	Mahapatra	METAGP: A PORTABLE, FULLY AUTOMATED PIPELINE FOR METAGENOMIC ANALYSES
#3	Selmi	NON-TARGETED LIPIDOMICS TO STUDY GUT MICROBIAL METABOLISM IN COLITIS
#4	Rabenow	GUT MICROBIOME AND HOST INTERACTION IN INFLAMMATORY ARTHRITIS AND ITS TREATMENT.
#5	Rüb	SEQUENCING-BASED QUANTITATIVE AND QUALITATIVE INVESTIGATION OF THE FECAL BACTERIAL AND FUNGAL MICROBIOTA IN PATIENTS WITH VARIOUS IMMUNE- AND GUT-RELATED DISEASES AND HEALTHY CONTROLS
#6	Balduin	COOPERATIVE PATHOGENICITY OF ENTEROPATHOGENIC E. COLI (EPEC) WITHIN MUCOSA-ATTACHED MICROCOLONIES
#7	Roese Mores	SEROLOGICAL CLASSIFICATION OF *ESCHERICHIA COLI* – PUTTING THE CAPSULAR POLYSACCHARIDE BACK ON THE MAP
#8	Zubiria-Barrera	INTERVENTION-DRIVEN MICROBIOME CHANGES AND ANTIBIOTIC RESISTANCE GENE DISSEMINATION IN PATIENTS WITH CYSTIC FIBROSIS
#9	Bos	SHORT- AND LONG-TERM EFFECTS OF ANTIBIOTIC THERAPY ON THE MYCOBIOME PATTERNS IN PATIENTS WITH CYSTIC FIBROSIS
#10	Frey-Wagner	*C. DIFFICILE* ABUNDANCE AND GUT MICROBIOTA COMPOSITION IN THE FIRST THREE WEEKS AFTER ANTIMICROBIAL TREATMENT FOR *C. DIFFICILE* INFECTION
#11	Mattner	RESOLUTION OF CHRONIC EPITHELIAL INFLAMMATION BY L-ARGININE SUPPLEMENTATION
#12	Kriegl	PERINATAL INTERACTION BETWEEN THE MICROBIOTA AND GUT MACROPHAGES WITH INTEGRATION OF GROUP B STREPTOCOCCI (GBS))
#13	Niedermeier	USING SYNTHETIC MICROBIAL COMMUNITIES AS A TOOL TO UNDERSTAND MECHANISMS OF STRAIN-STRAIN INTERACTIONS
#14	Pourjam	INVESTIGATING THE IMPLICIT DIVERSITY OF THE *MORAXELLACEAE* FAMILY USING THE TAXONOMY INFORMED CLUSTERING (TIC) ALGORITHM
#15	Rössler	IDENTIFICATION OF MICROBIOTA-DEPENDENT MECHANISMS GOVERNING AHR-DEPENDENT INFLAMMATION
#16	Amar	CUTANEOUS MICROBIOMES OF HIDRADENITIS SUPPURATIVA AND DARIER' DISEASE SHOW UNIQUE PATTERNS OF MICROBIAL DYSBIOSIS
#17	Weber	MICROBIAL ENERGY IN IMMUNE HOMEOSTASIS
#18	van Best	HOST FACTORS DRIVING GUT MICROBIOME MATURATION IN EARLY LIFE
#19	Magel	NFDI4MICROBIOTA: TOWARDS FAIR AND COMPREHENSIVE DATA IN MICROBIOME RESEARCH
#20	Jung	EXPLORING THE ROLE OF EVOLUTION IN RESISTANCE AND RESILIENCE OF GUT BACTERIA TO ANTIBIOTICS

ABSTRACT COLLECTION

SYSTEMS ECOLOGY OF THE HUMAN EXPOSOME

Paul Wilmes[1,2]

[1]Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Luxembourg
[2]Department of Life Sciences and Medicine, Faculty of Science, Technology and Medicine, University of Luxembourg, Luxembourg

The human microbiome represents a complex ecosystem which, through its emergent properties, contributes essential functions to its host. Recent large-scale metagenomic studies have provided insights into its functional potential but have mostly focused on taxa-centric views. However, the functional repertoire which is actually contributed to human physiology remains largely unexplored. For example, the human microbiome produces a complex biomolecular cocktail in the form of soluble nucleic acids, (poly-)peptides and metabolites, recently defined as the expobiome. This cocktail has many bioactive properties but these have so far eluded systematic study. This overall gap in knowledge is limiting our understanding of the role of the human microbiome in governing human physiology and how changes to the microbiome impact chronic diseases including metabolic and neurological conditions through the triggering and exacerbation of disease pathways. Furthermore, without mechanistic understanding of the microbiome's molecular complex, we are unable to rationally design microbiome-targeted therapies. In this context, the microbiome also represents a treasure trove for leads for the development of future diagnostic and therapeutic applications for chronic diseases. I will describe the current state of understanding of the functional microbiome in contrast to taxonomic views with a specific focus on microbiome-derived molecules in immune system stimulation and regulation. Ranging from systematic integrated multi-omic analyses of the microbiome-borne molecular complex to mechanistic studies in novel experimental systems, a clear roadmap towards translating the functional ecology of the gut microbiome into novel diagnostic applications and drugs will be drawn.

EVALUATING THE EFFECT OF CANDIDATE PREBIOTICS IN THE HUMAN GUT MICROBIOTA BY ACTIVITY-BASED CELL SORTING AND TARGETED ISOLATION

Hamid Rasoulimehrabani[1], Alessandra Riva[1], Deniz Inan[1], Bela Hausmann[2,3], Georgi Nikolov[1] and David Berry[1,2]

[1]Center for Microbiology and Environmental Systems Science, Department of Microbiology and Ecosystem Science, Division of Microbial Ecology, University of Vienna, Austria
[2]Joint Microbiome Facility of the Medical University of Vienna and the University of Vienna, Austria
[3]Department of Laboratory Medicine, Medical University of Vienna, Austria

Prebiotics are dietary supplements claimed to selectively promote the growth of beneficial gut bacteria. However, the selectivity of many candidate prebiotics has not been thoroughly investigated. This project focused on the selectivity of two candidate prebiotics - xylooligosaccharides (XOS) and lactulose - in the human fecal microbiota using activity-based sorting, 16S rRNA gene amplicon sequencing, and targeted isolation and cultivation.

To identify the metabolic activity of gut microbes on the single-cell level, human fecal samples were incubated in the presence of two cellular activity markers L-Azidohomoalanine (AHA) and heavy water (D2O). In this project, we identified the metabolically-active taxa that utilized XOS and lactulose using single-cell stable isotope probing (SIP), Raman activated cell sorting (RACS), and biorthogonal non-canonical amino acid (BONCAT) fluorescence tagging combined with fluorescence-activated cell sorting (FACS).

We found that members of the Firmicutes, Actinobacteria, and Bacteroidetes phyla responded to lactulose and XOS amendment after six hours of incubation. In addition, the relative abundance of Bifidobacterium and Blautia in the BONCAT positive fraction increased compared to the initial timepoint (0 hours). The use of heavy water-SIP combined with RACS allowed us to directly isolate members of the genera Lactococcus, Ruminococcus, Bifidobacterium, and Collinsella as utilizers of the added compounds.

Our research provided novel insights on the specificity of the dietary compounds XOS and lactulose that stimulate the metabolic activity of different taxa belonging to the major bacterial phyla of the human gut microbiota.

BLAUTIA PSEUDOCOCCOIDES AND *ENTEROCLOSTER CLOSTRIDIOFORMIS* CONFER COLONIZATION RESISTANCE AGAINST SEGMENTED FILAMENTOUS BACTERIA

Silvia Bolsega[1], Anna Smoczek[1], Tim Scheele[1], André Bleich[1], Bärbel Stecher[2,3], and Marijana Basic[1]

[1]*Institute for Laboratory Animal Science and Central Animal Facility, Hannover Medical School, Germany*
[2]*Max von Pettenkofer Institute of Hygiene and Medical Microbiology, Faculty of Medicine, LMU Munich, Germany*
[3]*German Center of Infection Research (DZIF), Partner Site Munich, Germany*

The intestinal microbiota forms a highly complex ecosystem of microorganisms that not only has a topical impact, but also influences the whole organism including host metabolism and immune system. One of the function of commensal microbes is to protect the gut from bacterial overgrowth and invading microbes. These microbial interactions known as colonization resistance are multi-faceted and include nutrient competition, metabolic competition, competitive niche exclusion, and induction of host immune response. In our previous study, we observed that established Oligo-Mouse-Microbiota12 (OMM12) exerts microbiota-mediated colonization resistance against segmented filamentous bacteria (SFB). SFB are gut commensals with comprehensive immunomodulatory features, which colonization can result in beneficial or detrimental health outcomes. Therefore, in this study we used gnotobiotic mice colonized with synthetic bacterial communities to investigate the role of commensal bacteria on the colonization behavior of SFB. To decipher the underlying mechanisms of preventing co-colonization, we aimed to detect candidate species by modifying the OMM12 consortium. OMM11 community, in which we excluded Akkermansia muciniphila YL44, was still providing colonization resistance towards SFB excluding the competition for ecological niche as a cause for colonization resistance. However, when excluding bacteria of Lachnospiraceae family, Blautia pseudococcoides YL58 and Enterocloster clostridioformis YL32, SFB could successfully colonize mice. Further experiments showed that both bacteria independently of each other and the whole community could prevent SFB colonization. Supplementation of spent growth media of YL58 and YL32 did not interfere with the SFB growth. Even though YL58 and YL32 are the major acetate producers, we could exclude acetate as well as changes in the luminal pH as factors mediating colonization resistance. Altogether, our results showed that both YL58 and YL32 are preventing enteric colonization of SFB through a still unknown mechanism.

THERAPEUTIC POTENTIAL OF TRADEOFFS DURING ADAPTATION OF *E. COLI* TO THE INFLAMED MOUSE GUT

Rahul Unni[1,2], Nadia Andrea Andreani[1,2], Daniel Unterweger[1,2], John Baines[1,2]

[1] *Max-Planck Institute for Evolutionary Biology, Plön, Germany*
[2] *Institute for Experimental Medicine, Kiel University, Kiel, Germany*

The basic evolutionary principle of adaptation by natural selection applies to the natural microbial populations in our microbiomes. Disease-mediated changes in the intestinal environment would impose different selection pressures on the microbiome to what we would expect in healthy individuals, resulting in selection for disease-specific microbial traits. Inflammatory bowel disease (IBD) results in drastic changes in the gut environment, and individuals with IBD are known to have significantly different microbiome compositions to healthy individuals.

In this study, we performed a long term in-vivo evolution experiment with *Escherichia coli* in a mouse model of IBD to study the adaptation of the gut microbiome to chronic inflammation within a host's lifetime. Bacteria were allowed to adapt to two alternative gnotobiotic mouse intestinal environments (healthy wild-type vs. inflamed *Il10*$^{-/-}$) for a period of three months, and fecal samples were regularly collected throughout the experimental period and analyzed by using a multi-omics approach. Populations derived from these fecal samples were used for systematically testing their metabolic repertoire in a range of metabolites using Biolog Gen III plates. Shotgun metagenomic sequencing was applied to identify loci that were significantly more or less mutated in the populations that evolved in the two mice genotypes. We identified a locus in the *E. coli* genome that may be associated with resistance to oxidative stress that is also differentially mutated in the *E. coli* populations that evolved in the *Il10*$^{-/-}$ mice. In addition, populations adapted to the *Il10*$^{-/-}$ mice were also significantly less capable of metabolizing a variety of antibiotics, includingfusidic acid.

In summary, we identified disease-specific bacterial traits that evolve in *E. coli* during adaptation to the chronically inflamed murine intestine. Notably, the evolution of such disease-specific traits is accompanied by tradeoffs that may be suitable for exploiting clinically, such as lower tolerance to antibiotics.

MOLECULAR SECRETS OF 7TH PANDEMIC *VIBRIO CHOLERAE*

Melanie Blokesch[1]

[1] Laboratory of Molecular Microbiology, Global Health Institute, School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland

The diarrheal disease cholera still sickens millions of people each year. Despite incredible progress in our understanding of *Vibrio cholerae*'s virulence mechanisms, studies on molecular processes that are not directly linked to the host remain limited for this pathogen.
In my talk, I will address this knowledge gap and present new insights into how the bacterium defends itself against mobile genetic elements such as plasmids and bacteriophages. Indeed, we recently identified two dedicated DNA defence modules (Ddm) in *V. cholerae* O1 El Tor strains, which are responsible for the ongoing 7th cholera pandemic. These systems are encoded on two major pathogenicity islands that are hallmarks of current pandemic strains. We show that both modules cooperate to rapidly eliminate small multi-copy plasmids by degradation. Moreover, one system can defend against bacteriophage infection by triggering cellular suicide (abortive infection; Abi). We go on to show that this Abi-like mechanism also increases the burden of large conjugative plasmids creating a fitness disadvantage that counter-selects against plasmid-carrying cells.
These two plasmid elimination strategies therefore answer the long-standing question of why plasmids, although abundant in environmental strains, are conspicuously absent from 7th pandemic *V. cholerae* patient isolates. Moreover, together with recent studies from other groups, our work highlights the importance of studying unknown genes and gene clusters that are located on prominent pathogenicity islands. Indeed, bacterial immune systems such as the ones described by our work, might have contributed to the success of the 7th pandemic clade of *V. cholerae*, which is considered the longest-enduring pandemic lineage in history.

CHRONIC EXPOSURE TO ANTISEIZURE DRUGS IMPACTS THE GUT MICROBIOTA COMMUNITY AND FUNCTION

Camille Dop[1], Stephane Auvin[2], Patricia Lepage[1], Zehra Esra Ilhan[1]

[1]Université Paris-Saclay, INRAE, AgroParisTech, Micalis Institute, Domaine de Vilvert, Jouy-en-Josas 78350, France
[2]APHP, Robert Debré University Hospital, Pediatric Neurology Department, Paris, France & Université de Paris, INSERM NeuroDiderot, Paris, France

Gut microbiota plays an essential role in the health and the development of the host. Diet and drugs are significant environmental factors affecting the microbiota composition. Exposure to drugs may lead to gut microbial dysbiosis. While the impact of some drugs, such as antibiotics, on the gut microbiome is widely recognized, the influence of chronically administered host-targeted drugs on the gut microbiome is less known. Our goal was to explore in vitro effects of chronic exposure to three antiseizure drugs (carbamazepine, valproate, and levetiracetam) on the gut microbial composition and metabolic functions.

Microcosms were established by cultivating four fecal inoculums from young children (11 months to 4 yo) over 24 hours. Using a semi-batch process, these fecal-derived microcosms were cultivated for 11 cycles (24 hours each) with the three antiseizure drugs or drug-free controls; the first seven cycles

with daily transfer to fresh media containing 2mM of the drugs, followed by four cycles of potential recovery period without any drugs. The impact of this exposure on the microbial community dynamics (diversity and composition) was determined by 16S rRNA gene sequencing of cycle 1 and 7 cultures. Metabolism of the microbial community after cycles 1 and 7 of exposure to carbamazepine was evaluated by a non-targeted metabolomics approach (LC-MS).

Our results show that semi-continuous cultivation strategy changed the overall microcosm composition during the first seven cycles until reaching a steady state. Carbamazepine had the most substantial impact on the gut microbiota structure and metabolism. More specifically, 9 genera including *Murimonas* and *Clostridium XIVa were positively* influenced by the carbamazepine exposure and 6 genera were negatively influenced such as *Faecalibacterium* and *Gemmiger* . We also observed that microbiome composition partially recovered after the four drug-free cycles. Finally, longitudinal exposure to carbamazepine modified the metabolic function of the microcosms by decreasing 52 metabolites that belong to Amino Acid, Carbohydrate, Cofactors and Vitamins Lipid, Energy, Nucleotide, Peptide and Xenobiotics super-pathways.

Understanding the longitudinal impact of antiseizure drugs on the gut microbiota may help develop modulation strategies to mitigate the treatment consequences on the gut microbiota and subsequently for the host health.

SYSTEMATICALLY INVESTIGATING THE INTERACTIONS BETWEEN THE GUT MICROBIOME AND PSYCHOTROPIC DRUGS

Lara Berg[1,2,3], Chiara Obermüller[1,2,3], Patrick Müller[1,2,3], Lisa Maier[1,2,3]

[1]Cluster of Excellence "Controlling Microbes to Fight Infections", University of Tübingen, Germany
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Mental illnesses continue to be a global health burden and only recently has the intimate physiological connection between the gut microbiome and brain become clear. Gut microbes not only affect host physiology, but also drug metabolism, and it has been demonstrated that the gut microbiome is particularly affected by antidepressant and antipsychotic drugs. As the gut microbiome plays a pivotal role in signaling across the gut-brain axis, it is plausible that the therapeutic and adverse effects of psychotropic drugs may be influenced by the microbiome. Consequently, interpersonal differences in treatment outcome (intensity, duration, onset, and side effects) may be explained by compositional variation of the microbiome from person to person.

To decipher the extent of these complex drug-microbiome interactions, a representative group of human gut bacterial species were tested in a high-throughput *in vitro* screening of over 1000 marketed drugs, which revealed a remarkably strong and direct antibacterial effect of antipsychotics on gut microbes. Following up on this therapeutic drug class, 1641 agents targeting neuronal signaling were tested on six phylogenetically diverse gut microbes, including commensals, pathobionts and pathogens. Approximately 14% of the 1614 compounds exhibited antibacterial potential against at least one of the tested strains. Interestingly, strains that play a crucial role in keeping the human gut healthy, such as butyrate and propionate producers, were significantly more inhibited by these compounds.

For the next step, 40 marketed antidepressants and antipsychotics have been chosen to be screened in both a synthetic model bacterial community and *ex vivo* (patient stool samples) complex microbiome communities. In order to comprehensively capture all possible interactions, the fate of all drugs across all communities will be mapped and the consequences of drug exposure on these communities will be charted using multi-omics approaches. This systematic interaction map will then serve as a starting point to mechanistically break down relevant interactions.

A detail understanding of the underlying mechanisms may create new opportunities to enhance treatment methods and foster the development of innovative microbial treatment strategies for mental illnesses.

DIFFERENTIAL IMPACT OF ANTIBIOTIC REGIMENTS DRIVE ON MICROBIOME ALTERATIONS AND EMERGENCE OF FUNGI

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***Background**:* The impact of antibiotic exposure on the gut microbiome and the detrimental effect of this impact on the human health has received broad attention in recent years, but research has focused on the bacterial flora or bacteriome in this context. Antibiotic induced alterations on the intestinal the mycobiome are not well studied.

***Methods**:* From a large prospective multicenter study (PILGRIM, NCT03765528), a subset of longitudinally collected samples from hospitalized patients fulfilling the following criteria were selected: antibacterial exposure (Abx) to at least one of the target antibiotics (cefuroxime, beta-lactam beta-lactamase inhibitor combinations [BLBLI], carbapenems, fluoroquinolones), no concurrent antifungal treatment except for prevention of oral candidiasis or micafungin. A control group consisted of patients without Abx. After DNA extraction, samples were subjected to shotgun metagenomics sequencing (Illumina NovaSeq platform).

***Results**:* We observed a decrease in bacterial alpha diversity when comparing samples after Abx to baseline samples, as previously described. These changes were more prominent in samples collected after BLBLI or carbapenem exposure than after the other antibiotic groups. We detected fungal sequences in 35/326 samples (10.7%) belonging mostly to Saccharomycetales with very low abundances a median of 0.03%. Of note, the frequency of the presence of fungal sequences was higher in samples after Abx (17.8%, 29/163) as compared to baseline or samples without Abx (3.7%, 6/163). Furthermore, presence of fungi was associated with a lower alpha diversity ($p<0.001$) and an increase in Enterococcaceae ($p<0.001$) in the corresponding samples.

Conclusions: We observe an impact of Abx on the mycobiome and an association between the presence of Enterococcaceae and fungi. This potential microbial interference warrants further investigation with regard to clinical outcomes.

PHAGE INDUCED STRAIN REPLACEMENT WITHIN MICROBIOMES

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Within the last decades microbiome research became more and more relevant to the field of public health. It vastly contributed to understanding the pathogenesis of major human diseases but also generated knowledge on the emergence and spread of antibiotic resistances (ABR). Nevertheless, new insights always open up more questions. An important one is: How can we use this knowledge to specifically eliminate harmful or ABR bacteria from the human gut without harming or disrupting overall microbiota composition?

To address this question, we focus on a new strategy termed “phage induced strain replacement within microbiomes”, which aims at combining phage- and probiotics-based therapy within one treatment. The idea behind this approach is to pose a fitness disadvantage on the targeted strain by a strain-specific phage cocktail and introduce a second, closely related, but phage-resistant competitor that competes for the same niche within the gut environment as the target strain. Ideally, this approach leads to strain replacement and elimination of the targeted strain without disturbing the overall gut microbiota composition. We focus on the three *species Escherichia coli, Enterococcus faecalis* and *Phocaeicola vulgatus* (formerly *Bacteroides vulgatus*). These species were chosen due to their clinical relevance, genetic diversity and high prevalence in the human gut.

We confirmed our theory in batch culture setups for *E. coli, P. vulgatus* and *E. faecalis*, showing that phage induced strain replacement is possible. Currently, we are establishing phage and competitor strain libraries for *E. faecalis* and *P. vulgatus* for subsequent experiments in a range of different environmental conditions in vitro and in vivo to further evaluate the potential efficiency of strain replacement as a new therapeutic approach to combat ABR and chronical intestinal disease

OPPOSING ROLES OF BACTERIAL MUCUS EROSION AND METABOLITE PRODUCTION IN INFLAMMATORY BOWEL DISEASE

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Bacteria and other microorganisms that compose the human gut microbiome play positive and negative roles in several diseases. Hundreds of genetic polymorphisms have been associated with predisposition to inflammatory bowel disease (IBD), but the mechanistic roles of diet and microbiome in precipitating inflammation in genetically susceptible hosts are largely unknown. We have elucidated pro- and anti-inflammatory contributions of the gut microbiome and dietary fiber—a broad class of mostly plant derived polysaccharides—in mice lacking the anti-inflammatory cytokine interleukin-10 (IL-10-/-). When deprived of dietary fiber, some gut bacteria resort to foraging on host mucus, leading to lethal colitis in IL-10-/- mice. Selective removal of mucus-degrading bacteria abrogates colitis, suggesting the requirement of mucus erosion for disease development. Likewise, genetic elimination of the mucus layer by deletion of the host gene (Muc2) that encodes the dominant secreted colonic mucin results in disease in mice fed a high fiber diet. Different disease severity develops in mice carrying human gut bacteria compared to those with a native specific pathogen free microbiota, further suggesting specificity of microbiota effects on host. When mice with human gut bacteria are weaned onto a low-fiber Exclusive Enteral Nutrition (EEN) diet often administered to IBD patients, IL-10-/- mice present less severe colitis than mice weaned onto the disease-promoting fiber-free diet. The microbiomes of EEN-fed mice revealed unexpected expansion of the non-mucin degrading, butyrate producer Eubacterium rectale and increased levels of the branch-chain fatty acid isobutyrate. Mice fed a disease-promoting fiber-free diet supplemented with isobutyrate develop less disease, suggesting that EEN reduces inflammation by supporting protective, isobutyrate-producing bacteria that counteract inflammation caused by mucus erosion. Eliminating E. rectale from the community eliminates elevated isobutyrate production. Our results highlight the concept that microbial functions should be the focus of positive and negative impacts in the development of IBD. Some of these functions (e.g., mucus degradation) can be genetically very complex and difficult to predict from taxonomic or metagenomic data, necessitating the use of simplified systems in which function can be discovered prior to investigating roles in humans. Thus, our study provides a potential path towards leveraging features of the IBD landscape that can be intentionally manipulated (diet & microbiome) to reduce the disease burden in people suffering from IBD.

ANTI-PHAGE MOLECULES PRODUCED BY BACTERIA

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Bacterial populations face the constant threat of viral predation exerted by bacteriophages (or phages). In response, bacteria have evolved a wide range of defense mechanisms against phage challenges. The currently known antiphage defense arsenal relies on a wide range of inhibitory mechanisms, but these are mainly mediated by protein effectors acting primarily at the cellular level. Recently, we showed that aminoglycosides, a well-known class of antibiotics produced by *Streptomyces*, are potent inhibitors of phage infection in diverse bacterial species. We demonstrate that aminoglycosides do not prevent the injection of phage DNA into bacterial cells, but instead block an early step of the viral life cycle, prior to genome replication. Strikingly, we show that acetylation of the aminoglycoside antibiotic apramycin abolishes its antibacterial effect, but retains its antiviral properties. Altogether, these results expand the knowledge of potential aminoglycoside functions in bacterial communities suggesting that aminoglycosides are not only used by their producers as toxic molecules against their bacterial competitors, but could also provide protection against the threat of phage predation at the community level.

BREAKING DOWN INFLAMMATORY BOWEL DISEASE: HOW METABOLIC MODELING SHEDS LIGHT ON THE GUT-MICROBIOME CONNECTION

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Inflammatory bowel disease (IBD) is characterized by a chronic inflammation of the gastrointestinal tract leading to severe gastrointestinal symptoms and significantly impacts patients' quality of life and life spans. The etiology of IBDs is not fully understood but results in an overly active immune response in the gut. It is believed that changes in the microbial composition of the intestinal tract play a role in the onset and progression of the disease.
In this study, we aimed to understand the metabolic changes associated with alterations in the microbial community and gut tissue during active inflammation in IBD patients undergoing anti-TNFα or anti-IL6 treatment. Using 16S, transcriptomic, and metabolomics data, we reconstructed metabolic models for the microbial community and gut tissue. To analyze these models, we applied different constrained-based modeling methods.
Our results showed a strong change in amino acid metabolism during periods of inflammation, promoted by changes in the metabolism of the bacterial community. Additionally, we observed significant changes in the interactions between the metabolism of bile acids and short-chain fatty acids between the host and bacteria during inflammation.
Furthermore, we found fewer metabolic changes for treatment response, but observed links between bacterial and host metabolism in sphingolipids, in amino acid and bile acid metabolism. We also associated changes in serum metabolites with IBD phenotypes and demonstrated that the predictions of metabolic modeling were reflected in the serum.
Finally, we used the bacterial models to predict dietary interventions that would affect the production/utilization of metabolites in the gut and promote healthier conditions.
Overall, our findings provide insight into the metabolic interactions between the gut microbiome and gut tissue in IBD patients and their potential contribution to inflammation, treatment response, and remission. We also present potential dietary interventions that could help shift these interactions back to healthier conditions.

CHARACTERIZATION OF TUMOR MICROBIOME USING SHOTGUN METAGENOME AND 16S RRNA GENE SEQUENCING

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Tumor microbiome, microorganism identified in tumor tissue, has great potential in treatment of tumors because they play a role in the formation of tumor microenvironment. Accurate and reliable characterization of tumor microbiome would not only help in better understanding of clinical features of tumor, tumorigenesis and progression but also treatment of tumors. Tumor microbiome remains challenging to investigate due to its low biomass. In addition, contamination of tumor microbiome from confounding bacterial DNA found in DNA extraction kits and environment can masks or alter the microbiota signal that may lead to erroneous results. Therefore, extensive and reliable method for DNA extraction of tumor microbiome needs to be established. Our study aims to accurately assess and characterize the microbial community of tumor microbiome. We also aim to use tumor microbiome to identify important biomarker and regulatory factor of cancer progression. Our study will gain more insights into the role of tumor microbiome in cancer development. In addition, better understating of tumor microbiome as indicator pathological types drug response and prognosis involves in tumor progression. Here, we employed multiple extensive methods to characterize tumor microbiome given the technical challenge due to its low biomass. Total genomic DNA were extracted using different commercial DNA extraction kits and phenol-chloroform reagent from mice and human tissues. We used negative controls and positive controls to detect contamination in the process of DNA extraction. Genomic DNA were then used for library construction and sent for shotgun metagenome and 16S rRNA gene sequencing. We used real-time quantitative PCR (qPCR) to quantify bacterial DNA. Shotgun metagenome sequencing results showed no contamination from the DNA extraction kits. Overall, it is important establish a reliable method to accurately characterize microbial community of tumor microbiome for clinical outcomes.

PROCESSED DIETS SHIFT THE INTESTINAL MICROBIOME AND EXACERBATE TUMORIGENESIS IN MURINE MODELS OF ATF6-DRIVEN COLON CANCER

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Introduction: The interplay between diet, host and intestinal microbiota plays a key role in colorectal cancer (CRC), with processed western diets (WD) of high fat and low fiber content as main contributors. The endoplasmic reticulum unfolded protein response effector activating transcription factor 6 (ATF6) is associated with early changes in CRC and colitis-associated cancer (CAC). We showed that murine intestinal epithelial cell specific expression of active ATF6 (nATF6) triggers spontaneous CRC (nATF6^{IEC}) and CAC (nATF6^{IEC} x IL10$^{-/-}$) in a microbiota-dependent manner.

Methods: To substantiate clinical relevance of ATF6 and validate nATF6-driven CRC and CAC mouse models, we performed human-derived fecal microbiota transfer (FMT) into germfree (GF) nATF6^{IEC} and nATF6^{IEC} x IL10$^{-/-}$ mice. To clarify the role of fat and fiber in tumorigenesis, mono- and biallelic nATF6^{IEC}, and monoallelic nATF6^{IEC} x IL10$^{-/-}$ mice were fed unprocessed chow or processed polymeric diets for 6 weeks after weaning. Microbial profiling and targeted metabolomics were performed to elucidate the impact of ATF6 and diets on the microbiome.

Results: CRC patient FMT established tumorigenesis in GF biallelic nATF6^{IEC} and monoallelic nATF6^{IEC} x IL10$^{-/-}$ mice that are otherwise tumor-free with luminal microbiota clustering according to donor. Compared to an unprocessed chow diet, the polymeric WD enriched in fat and depleted in fermentable fiber, increased tumor load in biallelic nATF6^{IEC} mice and tumor incidence in monoallelic nATF6^{IEC} x IL10$^{-/-}$ mice. Unexpectedly, the highly processed WD induced *de novo* tumorigenesis in otherwise tumor-free monoallelic nATF6^{IEC} mice. To understand the impact of high fat in this context, we modified the WD by lowering fat content or by supplementing with fermentable fiber. The absence of fermentable fiber in the polymeric diet already accelerated tumor load as well as *de novo* tumorigenesis. Surprisingly, fiber supplementation failed to protect the WD-induced tumorigenic phenotype despite microbial and metabolic changes. High fermentable fiber content in the low-fat diet even exacerbated nATF6-driven tumorigenesis, suggesting a tumor promoting rather than tumor protective function of fermentable fiber in processed diets. Microbial profiling revealed strong effects of the processed diets on the luminal microbiome with no clear effect of dietary fat or fiber. Moreover, the impact of tumor development on microbial communities was evident also on functional level by alterations in short chain fatty acids.

Conclusion: These findings highlight the ability of all processed diets to exacerbate nATF6-related tumorigenesis, with dietary fermentable fiber unexpectedly acting as a tumor driver. This implies that plant-derived metabolites of unprocessed chow diet may fulfill protective functions in our mouse models.

HOST-MICROBIOME INTERACTIONS IN THE CONTEXT OF RECENT HUMAN EVOLUTION

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Concurrent with urbanization and industrialization of lifestyles, the human gut microbiome dramatically shifts in composition and diversity. However, to what extent lifestyles transition impacts host-microbiome interactions and host physiology is unknown. In 2016, we founded the Global Microbiome Conservancy a non-profit initiative to 1) preserve the biodiversity of the human gut microbiome, 2) characterize its evolution across populations and host lifestyles and 3) investigate its interactions with the human host. We generated gut microbiome multiomics data coupled with host DNA and physiology data from dozens of populations worldwide, ranging from gatherers to fully industrialized groups. Leveraging these resources, we show that intestinal inflammation, humoral immune response, and patterns of horizontal gene transfers (HGT) between bacteria strongly associate with the host lifestyle. We reveal that gut microbiomes of industrialized individuals associate with elevated secretion of intestinal immunoglobulin A, despite lower levels of parasitic incidence. Furthermore, populations with gatherer lifestyles exhibit the lowest levels of intestinal inflammation. Finally, we show that gut bacteria within the microbiome of industrialized individuals exchange genes more frequently than in non-industrialized populations, potentially in response to increased environmental perturbations. Overall, our results suggest that industrialization of lifestyles perturbs our gut ecosystem and homeostasis on many levels, which could contribute to chronic inflammation diseases.

THE EFFECT OF KETOGENIC DIET ON THE HOST MICROBIOTA, IMMUNE AND CENTRAL NERVOUS SYSTEM

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The central nervous system (CNS) and the intestine communicate via peripheral nervous structures, the immune system and via intestinal microbial products and metabolites, building a bidirectional network called gut-microbiota-brain (GMB) axis. The microbiota is highly influenced by the dietary habits of the host. Ketogenic diet (KD) not only changes the microbiota composition but ameliorates conditions in several metabolic and neurologic diseases. However, the mechanisms behind the effect of this dietary intervention are not well understood. We aim to unravel the effects of KD on the function of gut microbiota and the host metabolism, the immune system and the CNS under healthy conditions. To study the microbiota, we performed 16S rRNA sequencing and metatranscriptomics on intestinal bacteria of mice colonized with a diverse and undefined microbiota (specific pathogen free, SPF) or with a gnotobiotic moderately diverse microbiota and fed purified KD or control diet. KD changed the

Firmicutes/Bacteroidetes ratio and the metabolism of Clostridia families. To investigate the effect of KD on the CNS in a microbiota-dependent and -independent way, we analysed the brain performing spatial transcriptomics in germ-free and SPF mice fed KD and control diet. In the brain, KD induced, in a microbiota-dependent manner, the upregulation of genes involved in neuronal cell communication and development, myelinization, and metabolic processes within specific areas, such as the hypothalamus, thalamus, amygdala and the hippocampus. We are currently investigating the effect of KD and microbiota on the host at the single cell level, via single nuclei RNA seq, in the affected brain areas and via flow-cytometry to identify the role of the immune system in our model. Behavioural tests will be performed to address the CNS functions in the different experimental conditions. Our experiments provide important findings to unravel the mechanisms behind the effects of KD on the host via the microbiota.

SYSTEMATIC MAPPING OF BACTERIAL CELL SURFACES

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The extracellular space separating microbes from their host represents the molecular forefront of host-microbe interactions. Its composition is arguably one of the most complex within the human body, and most poorly understood. Proteins displayed on microbial cell surfaces serve as a major component of this space and can play fundamental roles in microbial nutrient foraging and innate immune recognition/evasion. Yet, methods to comprehensively map the repertoire of cell-surface exposed proteins in commensal gut bacteria have been lacking. Here we have developed a proteome-wide approach to map which proteins are exposed on bacterial cell surfaces. By shaving the surfaces of highly abundant and prevalent gut commensal species (*Phocaeicola vulgatus* and *Bacteroides uniformis*) with proteases and coupling to LC-MS/MS, we have gained first insights into the surface proteome of these species. Our work represents a first global overview of cell-surface structures present in commensal gut bacteria, serving as a blueprint for understanding the machinery gut bacteria use to survive within the gut and the epitopes available to the host immune system.

KEY DETERMINANTS OF FMT SUCCESS

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Fecal microbiota transplantation (FMT) has achieved satisfactory results in preventing the recurrence of Clostridioides difficile infection, but these positive outcomes have only been partially replicated in other diseases. Several factors influence FMT success, including those related to donors and recipients (including diversity and specific composition of the gut microbiome, immune system, and host genetics) as well as to working protocols (fecal amount and number of infusions, route of delivery, and adjuvant treatments). Moreover, initial evidence suggests that the clinical success of FMT may be related to the degree of donor microbial engraftment. The application of cutting-edge technologies for microbiome assessment, along with changes in the current vision of fecal transplants, are expected to improve FMT protocols and outcomes.
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SPIKE-IN QUANTIFICATION TECHNIQUES FOR IMPROVED MICROBIOME SEQUENCING: SHORT- AND LONG-READ APPLICATIONS

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Advances in high-throughput sequencing technologies have enabled deep insights into the composition and functional capacities of the human microbiome in health and disease. In the context of the compositional data structure of standard sequence-based microbiome analysis and its impact on the detection of quantitative changes in individual microorganisms, we evaluated and compared different methods for absolute quantification of bacterial species within a complex matrix. To test this, we used a Latin square experimental design with varying amounts of both spike-ins and stool background. Exogenous organisms were spiked at quantified levels to comprehensively evaluate their quantitative recovery at different taxonomic resolutions. Species-specific real-time quantitative PCR (qPCR) and digital PCR (dPCR) were compared with relative and SCML-normalised abundances derived from 16S rDNA-based amplicon and shotgun metagenome sequencing using both long and short read technologies. We found that qPCR followed by dPCR provided the best representation of expected absolute gene copy numbers. Whole shotgun metagenomic sequencing was found to be more consistent with expected abundances compared to 16S rDNA-based amplicon sequencing, and quantitative recovery could be improved after spike-in normalisation of both amplicon and shotgun-based approaches.

By applying long-read-based shotgun metagenomic sequencing using a PromethION instrument (Oxford Nanopore Technologies), we were able to further evaluate the application and accuracy of this recently developed technology for the identification and quantification of bacterial strains within a complex microbiome. New technologies, such as nanopore sequencing, have the potential to improve resolution at the sequence level, which could lead to even more accurate analysis of the human microbiome. However, this will only be the case if potential sources of error are accurately identified and made verifiable through the implementation of appropriate controls.

DERIVING AND EVALUATING MICROBIAL PROFILES OBTAINED ACROSS DIVERSE SEQUENCING TECHNOLOGIES

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Microbiome profiling is a powerful method for understanding the composition and function of microbial communities. Two popular techniques used for that are 16S rRNA gene amplicon sequencing (16S-Seq) and shotgun metagenomics sequencing (SMG-Seq). While both methods offer unique advantages, for large-scale meta-analysis it is important to assess how robust and comparable the resulting microbial profiles are. However, differences in the sequencing methods and bioinformatics pipelines used can lead to discrepancies in the resulting microbial profiles. This study aimed to derive microbial profiles across different technologies, specifically 16S-Seq and SMG-Seq, and to evaluate the robustness of microbial disease signatures obtained with either technology.

To evaluate the robustness of microbial signatures obtained through diverse sequencing technologies and sampling types, a comprehensive microbiome meta-analysis was conducted which included publicly available colorectal cancer (CRC) datasets generated using both 16S-Seq and SMG-Seq. Data from a total of over 9,000 samples from both tissue and stool were obtained from 33 cohorts and were subsequently analyzed to evaluate the robustness of microbial CRC signatures across diverse sequencing technologies and sample types.

The findings of our analysis indicate that both 16S rRNA sequencing and shotgun metagenomics sequencing are effective tools for elucidating CRC-specific alterations in stool and tissue-associated microbial communities. However, while broadly similar, the microbial profiles derived from different methods and sample types differ in specific aspects. This can in part be attributed to technical factors such as variations in taxonomic resolution, sequencing depth, and sequencing biases. In part the observed differences are also due to biological and clinical differences between sample origin. Based on the overall broad similarity of CRC signatures across different sampling types and sequencing technologies we show that machine-learning (penalized logistic regression classifiers) can recognize consistent CRC differences in discriminating between CRC patients and controls across heterogeneous study populations and assay types used for microbiome profiling.

TOWARDS REAL-TIME IMAGING OF THE GUT MICROBIOME

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The gastrointestinal tract contains a complex ecosystem of microorganisms, characterized by microbe-host and microbe-microbe interactions. A balanced microbiome has been identified as critical to host health, with its dysbiosis implicated in various life-threatening diseases. Hampered by a shortage of quantitative species-specific in vivo visualization tools, our understanding of the protective mechanism of a balanced microbiome is still largely superficial. Recently, metabolic oligosaccharide engineering (MOE) combined with biorthogonal click chemistry (BCC) enabled species-specific labelling techniques have emerged. This approach has been used to successfully image the distribution of the commensal Bacteroides fragilis fluorescently in vivo, following an in vitro click chemistry reaction with a fluorescent probe (1). Additionally, the first example of MOE-BCC for PET imaging of Bacteroides fragilis colonization was performed in 2020, however this only allowed for a limited imaging time window due to the in vitro labeling strategy and radioisotope decay time (2). In this study, we aim establish a novel preclinical Positron Emission Tomography (PET) imaging method based on metabolic oligosaccharide engineering in combination with biorthogonal click chemistry labelling techniques. The combination of PET with the MOE-BCC reaction should provide a selective, quantitative imaging method for in vivo bacterial imaging, with increased resolution and imaging depth from the techniques previously used. Toward this end, a toolbox for the MOE-BCC labelling reaction has been established in the commensal Escherichia coli Nissle (EcN). Azide functional groups were integrated into EcN's newly synthesized polysaccharides through supplementation of the bacterial growth medium with azide-modified sugars. A variety of azidosugars and incubation conditions were tested to allow for optimization of the protocol. Verification of the labelling efficiency was performed by clicking of the Dibenzocyclooctyne (DBCO) conjugated fluorescent probe Alexa Fluor 647 and carrying out fluorescence measurements using Fluorescence-activated cell sorting (FACS). Thus far, within a 15 minute to 4-hour incubation window, 100% binding of the DBCO-conjugated probe to the azide-modified mannosamine and galactosamine analogs has been achieved. In the future, this study aims to extend the MOE-BCC based protocol to a Salmonella enterica Serovar Typhimurium (S. Tm) infection model, labelling in vivo with the radiotracer 64Cu-DBCO to enable PET/Magnetic Resonance imaging. This will further be applied to a secondary part of the study investigating the use of the probiotic EcN or the prebiotic fructooligosaccharide for S. Tm infection modulation. Once completed, this study will provide a toolbox for the in vivo, quantitative, GMO-free, species-specific bacterial imaging of EcN and S. Tm, with potential translatability to other bacteria.

Ref.: (1) Geva-Zatorsky et al. Nat Med. 2015; 21(9): 1091-1100. (2) Wang et al. Eur J Nucl Med Mol Imaging. 2020; 47(4): 991-1002.

INVESTIGATING THE MODE OF ACTION OF NON-ANTIBIOTIC DRUGS ON HUMAN GUT MICROBES BY MICROSCOPY

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Consumption of non-antibiotic human-targeted drugs (HTDs) has been shown to have a major impact on the composition of the human gut microbiome. To date, however, little is known about the exact mechanisms of how HTDs directly influence the physiology and growth of gut bacteria. In part, this is because many of the effects cannot be observed and studied in classical model organisms, while detailed studies of the mode of action in gut bacteria themselves are hampered by the anaerobic growth conditions of these bacteria.

Brightfield fluorescence microscopy is routinely employed in antibiotic research to provide quantitative insight into the cellular and molecular responses of bacteria to drugs. Fluorescent dyes, such as DAPI and FM lipophilic styryl dyes are used to visualise the structure and integrity of DNA and cell membranes, respectively. Effects on cell viability or membrane potential can be revealed using propidium iodide or DiBAC dyes.

To establish such fluorescence microscopy assays for anaerobic microbes, we first selected seven common and abundant anaerobic bacterial species of the human gut microbiome. For these species, we optimised sample preparation, staining and fixation methods for FM 5-95, FM 4-64FX and DAPI under anaerobic conditions. As controls, we used nisin, an antibacterial peptide known to generate pores in the membrane, and CCCP and valinomycin, which act as ionophores and disrupt the membrane potential. As a proof of concept, we selected six HTDs from different therapeutic classes that have been shown to inhibit the growth of the species we selected. We determined their minimum inhibitory concentration to characterize their physiological consequences in a concentration-dependent manner using fluorescence microscopy. In a next step, we aim to implement detailed quantification, time-resolved data acquisition and higher sample throughput in order to be able to systematically extend our analyses to additional species and drug classes.

Overall, our fluorescence microscopy assays enable a meaningful investigation of specific cellular processes in anaerobic bacteria. They can be used to decipher the physiological consequences of HTD on individual species of the human gut microbiome. In the long term, this will allow us to better understand the consequences of drug therapy on the gut microbiome.

EFFECT OF EARLY LIFE COLONIZATION BY FLAGELLATED BACTERIA ON ENTERIC EPITHELIAL CELL RESPONSES AND MICROBIOME ESTABLISHMENT

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The neonatal period is essential for the establishment of microbiome-host interactions and TLR5 was shown to influence microbiota development. However, mechanistic understanding of the underlying processes is incomplete. We used a gnotobiotic approach combined with multi-Omics sequencing to study the impact of flagellated bacteria on host and microbiota development.

A collection of 21 *Escherichia coli* strains from the mouse intestine was screened for differential expression of flagellin and susceptibility to phages. Germfree mice were colonized with nine non-flagellated bacteria from the synthetic community Oligo-Mouse Microbiota (OMM9 model) in the presence or absence of the flagellated *E. coli* strain DSM112117 or a non-flagellated isogenic mutant thereof, hereon referred to as ΔfliC. The gnotobiotic mice were mated to generate offspring colonized from birth to emulate natural colonization processes. The study included two arms (n=8/group): mice in arm 1 were culled after one week to study effects on the neonatal gut epithelium; mice in arm 2 were colonized additionally with SPF microbiota at 4 weeks of age and culled after eight weeks to determine effects of the early life synthetic communities on strain engraftment. At 7 days of age, 16S rRNA amplicon profiles revealed the dominance of *Enterococcus faecalis* (nearly 100% relative abundance, with very low amount of *Blautia pseudococcoides*) in the small intestine of OMM9 mice. The relative abundance of *E. faecalis* decreased substantially in the presence of *E. coli* (both wildtype and mutant strain). Single-cell RNA-sequencing of epithelial cells isolated from the small intestine of 7-day old mice showed clear transcription profiles linked to flagellated *E. coli* when compared to ΔfliC. Genes involved in inflammatory pathways, apoptosis, lysosome, ferroptosis, and antigen processing and presentation were upregulated in mice colonized with OMM9 + flagellated *E. coli.* In contrast, mice colonized only with OMM9 and OMM9 + ΔfliC showed upregulated genes involved in fat digestion and absorption and oxidative phosphorylation pathways. The Apolipoprotein C-II, known as an essential cofactor for lipoprotein lipase activity, was characterized by highly significant upregulation in these two colonization groups.

Communities in the small intestine and caecum of the adult mice in arm 2 of the study have been sequenced (n=96). Metagenomic and metatranscriptomic analyses are ongoing to determine the effects of early life exposure to flagellin on strain engraftment and microbiome functions.

T CELL SKEWING IN RELATION TO INTESTINAL DYSBIOSIS AND GRAFT-VERSUS-HOST DISEASE IN ALLOGENEIC STEM CELL TRANSPLANTATION

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Allogeneic hematopoietic stem cell transplantation (aHSCT) is a promising treatment option for hematological malignancies, but the success of the treatment remains limited by the risk of graft-versus-host disease (GvHD). GvHD is a severe complication of aHSCT and gastrointestinal manifestations of GvHD are the main reason for transplantation-related mortality. The mechanisms that initiate and promote inflammation in the course of alloreaction are still not completely understood, but first observational correlations to the patient's microbiome have been made. Antibiotic treatment cause severe dysbiosis in the intestinal microbiota, which associates with increased incidence of GvHD and GvHD-related mortality.
A central hypothesis of our project is that microbiome-derived antigens and/or their metabolites affect donor T cell activation and skew the reconstitution of regulatory immune responses in the gut. To investigate this hypothesis, we took advantage of a globally unique aHSCT patient biosample collection. We combined multiplexed tissue imaging and single-cell RNA sequencing on gastrointestinal biopsies from aHSCT patients with fecal microbiome analysis to study the relationship between the intestinal microbiome, mucosal lymphocyte populations and T cell receptor diversity in patients with or without GvHD and upon therapeutic interventions such as antibiotic treatment and fecal microbiota transplantation. The presence of suppressive Tregs was linked to a high microbiota diversity and short-chain fatty acid-producing bacteria, but negatively correlated with GvHD severity. Furthermore, GvHD severity was strongly associated with the clonal expansion of CD8+ T cells, which were found distributed over anatomically distant regions of the gut and persistent over time. To decipher the antigen source driving the clonal CD8+ T cell expansion we currently re-express GvHD-associated TCRs identified by scRNAseq in the Jurkat cell line and screen the TCRs for reactivity against potential antigens. Identifying the targets of expanded CD8+ T cells would be a new landmark in the understanding of GvHD pathophysiology and support the further development of microbiome interventions as a treatment for GvHD.

HELICOBACTER PYLORI PROMOTES COLORECTAL CARCINOGENESIS BY DEREGULATING INTESTINAL IMMUNITY AND INDUCING A MUCUS-DEGRADING MICROBIOTA SIGNATURE

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Helicobacter pylori infection is the most prevalent bacterial infection worldwide. Besides being the most important risk factor for gastric cancer development, epidemiological data show a nearly twofold increased risk for infected individuals to develop colorectal cancer (CRC). However, a direct causal and functional link between *H. pylori* infection and CRC was so far lacking.

We infected Apc-mutant mouse models and C57BL/6 mice with *H. pylori* and conducted a comprehensive analysis of *H. pylori*-induced changes in intestinal immune responses and epithelial signatures via flow cytometry, chip cytometry, immunohistochemistry and single cell RNA sequencing. Microbial signatures were characterized and evaluated in germ-free mice and via stool transfer experiments. In addition, we infected Apc-mutant mice with an *H. pylori* strain which lacks the virulence factor cytotoxin associated gene A (CagA) to assess its impact on colon tumorigenesis.

H. pylori infection accelerated tumor development in Apc-mutant mice. We identified an altered immune signature in the intestinal and colonic epithelium characterized by a reduction in regulatory T cells, pro-inflammatory T cells and pro-carcinogenic STAT3 signaling, as well as a loss of goblet cells. These changes, together with a pro-inflammatory and mucus degrading microbial signature, contributed to tumor development. Similar immune and epithelial alterations were found in human colon biopsies from *H. pylori*-infected patients. Housing of Apc-mutant mice under germ-free conditions ameliorated, and early antibiotic eradication of *H. pylori* infection normalized the tumor incidence to the level of uninfected controls. Moreover, the *H. pylori* CagA-mutant strain was not as potent in inducing the pro-carcinogenic and pro-inflammatory phenotype seen after infection with a CagA-proficient strain. As this phenotype was also transmissible via stool transfer, a CagA-dependent shaping of the intestinal microbiota is suggested.

Our studies provide evidence that *H. pylori* infection is a strong causal promoter of colorectal carcinogenesis and that these tumor-promoting effects are largely dependent on its virulence factor CagA. Eradication of *H. pylori* infection by antibiotic treatment prevented inflammation and colon tumorigenesis. Therefore, implementation of H. pylori and CagA status into CRC

prevention programs should be considered. Our current research effort aims at identifying a pro-carcinogenic bacterial consortium in human *H. pylori* infected CRC patients, as well as elucidating if antibiotic therapy after chronic *H. pylori* infection can still prevent colon carcinogenesis and might be an effective measure to reduce risk.

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NITROGEN CYCLING IN THE HUMAN GUT MICROBIOME ACROSS AGES OF LIFE

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Nitrogen exchange between the human host and the gut microbiome is tightly regulated depending on both bacterial and host requirements and varies across age. Although gut bacteria are known to contribute to blood ammonia level and inform microbiome-targeted treatments for hyperammonemic states, a species- and genome-resolved map of nitrogen metabolism in the gut is lacking. This knowledge gap leaves open questions: (i) How are key nitrogen metabolic functions distributed across gut bacterial species and strains? (ii) How do these functions equilibrate across age and according to the host's biosynthetic needs? (iii) Which species act as ammonia sinks or producers in health and disease? Here, we provide the first genome-resolved systematic characterisation of the genetic repertoire of the human gut microbiome involved in organic nitrogen synthesis, degradation and cycling, using >13,000 globally distributed samples from 62 metagenomic studies. We systematically mapped known and predicted genes responsible for ammonia-production and recycling, identifying distinct metagenomic signatures across early and adult-life microbiomes. In particular, during early life, when nitrogen requirements and blood ammonia levels are higher, the gut microbiome is rich in organic nitrogen degradation functions (e.g. urease) that can contribute to ammonia production. We further explored differences in gut nitrogen metabolic functions across health and disease, focusing on host genetic and acquired bottlenecks in ammonia excretion (e.g. urea cycle disorders and liver failure). We identified key alterations in the gut nitrogen salvage and degradation functions in these conditions, confirming and mechanistically characterising the role of gut dysbiosis in their pathogenesis. By integrating our species-resolved map of nitrogen metabolism and published data on the antibiotic susceptibility of gut microbiome species, we investigated the specificity of antibiotics that are commonly used to treat hyperammonemic states, providing a rational ground for these treatments and proposing their refinement to selectively target ammonia-producing species.

METAGP: A PORTABLE, FULLY AUTOMATED PIPELINE FOR METAGENOMIC ANALYSES

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Since the completion of the Human Genome Project, the cost of next-generation (NGS) sequencing has decreased drastically, outpacing even Moore's law. Therefore, the metagenomic sequencing has become standard procedure for analyzing the structure and functionality of microbiomes. Aside from the simply overwhelming amount of data, a metagenomic analysis is a complex task comprising several, yet non-standardized steps, involving different software tools whose results are often not directly compatible. Unlike 16S rRNA gene amplicon sequences, metagenomics data are much larger in terms of number of reads. Therefore, dealing with several metagenomics data is an intensive process concerning computational power and processing time. Due to these reasons, to perform an analysis consists of multiple steps and different software tools, it can be intimidating for non-expert users and requires a good programming knowledge. Thus, we developed a metagenomics analysis pipeline, which should be usable by non-expert bioinformatic users, but still have sufficient power and flexibility of handling each different project needs. Here we present the *MetaGP* pipeline, developed in the Python environment by covering all possible steps for downstream analysis of the shotgun metagenomics data. This includes contamination filtering, quality control, computing the abundance of bacteria, normalization, alpha- and beta-diversity analysis, determining the taxonomic profile up to the bacterial strains level, assembly of the reads to contigs, and determining functional profiles. Since the analysis is intensive concerning processing time, MetaGP utilizes the available computer resource simultaneously by using the parallel processing technique to speed up the process. MetaGP has been developed to execute automatically all necessary steps after providing metagenomic data as input. Therefore, it is easy to use for the beginners, but can also be a framework for the advanced users who can modify settings or expand the tool by taking advantage of the modular architecture of the tool. Thus, MetaGP is able to be upgraded in future continuously, implementing further downstream analyses by following the requirements of the research community.

NON-TARGETED LIPIDOMICS TO STUDY GUT MICROBIAL METABOLISM IN COLITIS

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Inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's Disease are chronic relapsing intestinal disorders driven by multiple factors such as genetics, environment, immune system, or microbes. A multitude of studies showed that IBD is associated with altered microbial composition and function. In this work, we used the *Citrobacter rodentium* model of infection to understand the role of the gut microbiota during infection. When the enteric pathogen *C.rodentium* colonizes gnotobiotic OMM[12] mice, which harbor a defined synthetic bacterial community, we observed a progressive increase of gut colonization associated with gut inflammation that culminates 10 days post-administration, followed by a progressive decrease associated with the resolution of inflammation at day 20. A non-targeted lipidomics approach based on liquid chromatography high-resolution mass spectrometry was conducted to investigate gut microbial lipid metabolism variations during colitis. Here, we provide detailed structural identification of bacterial and host-derived lipids and characterize inflammation-associated lipid changes. Multivariate statistical analysis was performed to study colitis's impact on lipid profiles. We found that host-derived lipids mainly glycerophospholipids and sphingolipids were significantly increased in inflamed mice accompanied by a decrease of bacterial lipids mainly produced by members of the phylum Bacteroidetes and Verrucomicrobiota. Lipidomic analysis revealed that several bacterial lipids are highly impacted by *C. rodentium* colonization. These bacterial lipids are dihydroceramide derivates and serine-dipeptide lipids produced by *Bacteroides* and ornithine lipids found in *Akkermansia*. Sphingolipids have been found in membranes and extracellular vesicles of Bacteroides and are important signaling molecules involved in regulating inflammation and immunity. We hypothesize that *Bacteroides* and *Akkermansia*-derived lipids are transported via bacterial extracellular vesicles into host intestinal epithelial tissue and liver and modulate host physiology. Further experiments will be performed to investigate the role of microbial lipids from extracellular vesicles in colitis.

GUT MICROBIOME AND HOST INTERACTION IN INFLAMMATORY ARTHRITIS AND ITS TREATMENT

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Millions of people worldwide suffer from rheumatic diseases, including rheumatoid arthritis (RA) and psoriatic arthritis (PsA). These systemic inflammatory diseases have an increasing incidence and there are no curative treatments available, thus, they contribute to the increasing burden on our health care system. The triggers for disease development are still not well understood. Genetic predispositions have been identified, but environmental factors that may influence the disease are also being investigated, including but not limited to the gut microbiome. Of note, conventional disease-modifying antirheumatic drugs (cDMARDs) such as methotrexate (MTX), which are used to treat RA and PsA patients have not only immunosuppressive effect, but microbiota-modulating effects have been described as well. Moreover, several studies have provided evidence that the composition of the gut microbiome may influence the efficacy of cDMARDs in RA. Due to the complex interactions between drugs and the microbiota, cross-sectional studies require large patient numbers to gain mechanistic insight into these process.

Therefore, we are recruiting newly diagnosed RA and PsA patients to the Rheuma-Vor cohort, in which they are longitudinally clinically monitored and regularly asked to submit stool samples for microbiome analysis. This enabled us to analyze microbiome composition and function before and after taking cDMARDs to analyse the impact of the drugs and to investigate whether specific microbiome features are associated to treatment success. We found that the response to MTX in PsA and RA patients is not dependent on microbial diversity; this does not differ between responders (R) and non-responders (NR). However, we demonstrated that the presence of different bacteria is related to clinical response to MTX. Bacterial species belonging to the *Lachnospiraceae* and *Clostridiaceae* families were enriched in PsA-R and RA-R. In addition, we demonstrated that increased numbers of bacteria involved in short-chain fatty acid (SCFA) production were present in responders. This could indicate that SCFAs positively influence the effect of MTX.

Together, our analysis reveals that microbiome features influence treatment response. By further identifying bacterial species that have a positive impact on MTX efficacy and characterizing their specific mechanism, predictions could be made as to which patients will respond to certain drugs and how to improve treatment responses.

SEQUENCING-BASED QUANTITATIVE AND QUALITATIVE INVESTIGATION OF THE FECAL BACTERIAL AND FUNGAL MICROBIOTA IN PATIENTS WITH VARIOUS IMMUNE- AND GUT-RELATED DISEASES AND HEALTHY CONTROLS

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Background: The human gut microbiota has been of great interest for researchers of various medical disciplines over the past years. Recently, scientific focus is shifting from a unidimensional view on the bacterial microbiota only to the inclusion of other microbial communities – in particular the fungal microbiota – in order to derive a better understanding of microbial networks and metabolisms and thus establish new diagnostic or even therapeutic tools on the long-term.

Patients and Methods: To determine transkingdom variations and quantitative relations in the fecal microbiota of patients with different immune- and gut-related diseases, 7 patient cohorts (irritable bowel syndrome, flatulence, ulcerative colitis, stem cell transplantation recipients, intensive care unit, HIV, vaginal candidiasis, recurrent *Clostridioides difficile* infection) of 9-11 patients each were recruited and asked to provide one fecal sample. Bacterial 16S and fungal ITS amplicons were sequenced on an Illumina Miseq System and patient samples were compared to the microbiota composition of healthy controls.

Results: An initial next generation co-sequencing analysis of the 16S and ITS genomic regions aiming to determine the quantitative relationship between bacterial and fungal communities revealed a strong overrepresentation of bacterial populations, only about 0.1% (or less) of obtained reads could be assigned to fungi. There were a few fecal samples containing >0.1% of fungal DNA, 5 belonged to patients with *Clostridioides difficile* infection, 3 to patients requiring intensive care treatment and 1 each belonged to patients with irritable bowel syndrome, HIV infection and leukemia after receiving allogenic stem cell transplantation. Each sample containing >0.1% of fungal DNA presented ITS-reads that could be assigned to one specific fungal species, indicating an overrepresentation of a fungal species in those samples. Taking a deeper look into mycobiome patterns using ITS-focused sequencing revealed

differences in the mycobiome composition of several patient cohorts compared to healthy controls. On genus level, a high abundance of *Candida* in patients with *Clostridioides difficile* infection and patients requiring intensive care treatment as well as an overrepresentation of *Saccharomyces* in patients with Ulcerative Colitis became evident.

Conclusion: Although fungi make up only a very small proportion of the intestinal microbiome, it is possible to identify associations between certain diseases and altered mycobiota, especially an overrepresentation of the genera *Candida* and *Saccharomyces*. This suggests that fungi, although quantitatively clearly inferior to bacteria, may have a greater influence on the microbiome and certain pathophysiological processes than initially suspected.

COOPERATIVE PATHOGENICITY OF ENTEROPATHOGENIC E. COLI (EPEC) WITHIN MUCOSA-ATTACHED MICROCOLONIES

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Enteropathogenic *Escherichia coli* (EPEC) remain a major cause of diarrheal disease in infants in developing countries. Hallmark of typical EPEC (tEPEC) infection is the formation of so-called attachment and effacement (A/E) lesions. Those are formed upon the tight attachment of bacteria that ultimately form dynamic multicellular bacterial consortia (microcolonies) at the surface of the host small intestinal mucosa. While the requirement of microcolony formation for tEPEC pathogenicity has been extensively studied, the actual architectural formation and development of EPEC microcolonies, including the transcriptional heterogeneity and cooperation between individual bacterium within those microcolonies, have not yet been addressed. Using various combinations of bacterial mutants, fluorescent gene expression and sensor reporter strains together with previously established *in vitro* (immortalized murine intestinal epithelial cells), *ex vivo* (murine intestinal organoids) and *in vivo* models, we aim to better understand, at the bacterial level, the mechanistic processes leading to microcolony formation, and ultimately to a successful infection. The results of our study should significantly improve our understanding of the cooperative effect of bacteria within multicellular consortia and their crucial contribution to EPEC colonisation, transmission and pathogenesis, and could lead to the development of new therapeutic strategies.

SEROLOGICAL CLASSIFICATION OF *ESCHERICHIA COLI* – PUTTING THE CAPSULAR POLYSACCHARIDE BACK ON THE MAP

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Escherichia coli is a common and generally benign colonizer of the human gut. However, certain strains cause serious infections and pose a significant health risk. The capsular polysaccharide (CPS), a major surface antigen and important virulence factor of pathogenic *E. coli*, is strongly associated with neonatal meningitis and has been reported as a common virulence determinant of Extraintestinal Pathogenic *Escherichia coli*. Despite this, the epidemiology of CPS in *E. coli* infections is poorly understood due to the limited use of *in vitro* serotyping, which is laborious, error-prone and costly. As an alternative, clinical and diagnostic laboratories have increasingly adopted whole genome sequencing (WGS)-based information to characterize bacterial isolates. However, the lack of classical CPS serotyping data for these isolates leaves a missing link between capsule types and their underlying genetics. Here, we aim to develop an *in silico* CPS typing method based on WGS data. To this end, we sequenced the entire CPS type strain collection from the Statens Serum Institut (Denmark) using a combination of PacBio/ONT and Illumina sequencing technologies. We extracted and annotated all CPS biosynthesis gene clusters and performed a biochemical verification of capsular polysaccharide structures using a novel labeling method. Our goal is to provide a genome sequencing-informed, robust and accurate alternative to classical serological CPS typing, enabling effective disease surveillance, outbreak detection, and accelerating the development of strategies for preventing and treating infections.

INTERVENTION-DRIVEN MICROBIOME CHANGES AND ANTIBIOTIC RESISTANCE GENE DISSEMINATION IN PATIENTS WITH CYSTIC FIBROSIS

Cristina Zubiria-Barrera[1,2], Tilman E. Klassert[1,2], Robert Neubert[1,2], Malena Bos[1,2], Jenny Fiebig[1,2], Michael Lorenz[3], Jochen G. Mainz[4], Hortense Slevogt[1,2].

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Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) affecting more than 100,000 individuals worldwide. These genetic mutational changes lead to malfunction of exocrine tissues and severe damage of the respiratory and digestive tracts. Recent therapeutic advances have increased the life expectancy of CF patients. However, recurrent pulmonary infections leading to acute pulmonary exacerbations and chronic inflammation often results in respiratory failure and significant morbidity. The frequent antibiotic interventions of these patients represent an important manipulation of the microbial communities in the already biased microbiome structures in different organs. The particular effects of long-term and short-term antibiotic treatments on the compositional microbiome changes and the potential accumulation of antibiotic resistance genes (ARGs) are yet largely unknown.

This study conducted a longitudinal analysis of the microbiome structures in CF patients' respiratory and gastrointestinal tracts, dividing patients into two cohorts based on disease severity and antibiotic administration (ambulant/per os vs. stationary/intravenous). Microbiome analyses were performed before and after therapeutic interventions for acute exacerbation episodes, and long-term therapeutic effects were monitored using clinical data on cumulative antibiotic intake over the previous three years. The study compared microbial community structures and detection rates of different ARGs between patient cohorts. Healthy controls and household relatives were further used as outgroups.

Regression models with different therapeutic variables identified specific microbiome and ARG dissemination patterns within the CF cohorts. This study contribute to a better understanding on the short- and long-term effect of antibiotic interventions on microbial community structures in different body sites of CF patients.

SHORT- AND LONG-TERM EFFECTS OF ANTIBIOTIC THERAPY ON THE MYCOBIOME PATTERNS IN PATIENTS WITH CYSTIC FIBROSIS

Cristina Zubiria-Barrera[1,2], Tilman E. Klassert[1,2], Malena Bos[1,2], Robert Neubert[1,2], Jenny Fiebig[1,2], Michael Lorenz[3], Jochen G. Mainz[4], Hortense Slevogt[1,2].

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Cystic Fibrosis (CF) is a prevalent genetic disease that affects around 100,000 people worldwide. It is a chronic, progressive multi-organ disease that is caused by dysfunction of the exocrine glands leading to thickened mucus. In the lungs, CF leads to recurrent lung infections and chronic inflammation, which cause respiratory failure and significant morbidity. While the bacterial microbiome in CF patients is well described, recent studies suggests that the fungal microbiome may also play an important role in disease pathogenesis and progression. However, many aspects of the fungal microbiome in CF remain poorly understood. Recent studies using sequencing approaches have shown that the fungal microbiota in CF patients' airways is more complex than previously expected. Although few studies have examined the occurrence and pathogenicity of fungi in CF patients' polymicrobial infections, there is evidence that the disease and its associated interventions, such as antibiotics and corticosteroids, might promote fungal colonization in the respiratory tract.

This study focused on characterizing the mycobiome of CF patients compared to healthy individuals and analyzing treatment-associated changes. These include the short-term effects of antibiotics on the mycobiome during acute treatment after clinical exacerbation and the long-term effects of cumulative antibiotic intake over a 3-year period. Thus, gut and nasal samples were collected at multiple time points, and fungal load was analyzed by qPCR, while ITS amplicon sequencing was used to analyze compositional aspects and diversity metrics. Our results showed that CF patients had significantly higher fungal loads in both stool and nasal lavage samples compared to the healthy group. In nasal samples, CF patients showed a significant increase of *Candida spp*., which was correlated with the cumulative antibiotic intake during previous years of therapy.

Overall, this study highlights the potential role of fungi in the pathophysiology and progression of CF and describes the site-specific effects of antibiotic treatment on fungal colonization patterns in CF patients.

C. DIFFICILE ABUNDANCE AND GUT MICROBIOTA COMPOSITION IN THE FIRST THREE WEEKS AFTER ANTIMICROBIAL TREATMENT FOR *C. DIFFICILE* INFECTION

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Background: Antimicrobial treatment is a major risk factor for development of *Clostridioides difficile* infection (CDI) and antimicrobial treatment for CDI further disturbs the endogenous gut microbiota, contributing to the risk of recurrent CDI (rCDI). Asymptomatic *C. difficile* colonization can be observed in 4-15% of healthy people. Yet, little is known about asymptomatic *C. difficile* colonization directly after treatment of a CDI episode. We aimed to study *C. difficile* abundance and gut microbiota composition in the first three weeks after antimicrobial treatment for CDI.

Methods: 14 CDI patients were enrolled for the study and fecal samples were collected on a weekly basis during the first three weeks after antimicrobial treatment for CDI. Clinical data, frequency of bowel movement and stool consistency were retrieved during telephone-follow ups on the same days as fecal sample collection. Gut microbiota composition and relative *C. difficile* abundance were studied by amplicon-based 16S rRNA sequencing with amplification of variable regions 1-9 (QIAseq® 16S/ITS panel, Qiagen) and paired end sequencing (2x300 nt) on an Illumina MiSeq instrument. Sequencing data was processed with an in house developed pipeline and NAMCO.

Results: Of 14 participants, one developed a rCDI during the study period. *C. difficile* was present with varying abundance in 85 % of participants at any of the timepoints for fecal sample collection one to three weeks after antimicrobial treatment for CDI. The relative abundance was ranging from 0.002 % to 37 % in *C. difficile* positive samples. At the last time-point still 58 % of samples remained positive for *C. difficile*. Mean gut microbiota alpha-diversity was lowest directly after antimicrobial treatment and increased over the three weeks study period, but not all participants showed a continuous increase.

Conclusion: Our results show that *C. difficile* can be detected with varying abundance in 65 % of samples in the first three weeks after CDI. Our findings provide the basis for further research into asymptomatic *C. difficile* colonization and the role of the endogenous gut microbiota for protection against rCDI.

RESOLUTION OF CHRONIC EPITHELIAL INFLAMMATION BY L-ARGININE SUPPLEMENTATION

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Inducible NO synthase (NOS2) and arginase (ARG) 1 compete for the semi-essential amino acid L-arginine as common substrate. Previous studies supported the concept that ARG1 promotes tissue repair and immunosuppression, whereas NOS2 perpetuates inflammatory immune reactions and causes immunopathology.

In contrast to the widely accepted immunosuppressive function of ARG1, we have recently made the unexpected observation that ARG1 acts as anti-resolvin in mouse models of DSS-induced or oxazolone-driven colitis. In both models, we identified the enzymatic consumption of L-arginine as driver of chronic epithelial inflammation. This conclusion results from the following findings: (1) Tek2- -driven deletion of ARG1 caused resolution of epithelial inflammation in both colitis models. (2) Changes in the composition of intestinal microbiota accompanied the deletion of ARG1. Transplantation of fecal microbiota from ARG1 knockout mice into wild type (WT) recipients promoted epithelial healing, whereas transfers from WT littermates into ARG1-deficient mice prevented an accelerated recovery of epithelial lesions. (3) Most importantly, dietary L-arginine supplementation induced resolution of colitis and enhanced the recovery from epithelial damage.

Based on these data, we postulate that dietary L-arginine therapy compensates for the deficiency of this versatile amino acid, which commonly occurs during epithelial inflammation. Whether L-arginine supplementation restrains dysregulated immune responses, corrects intestinal dysbiosis and heals epithelial lesions in clinics is subject of further investigation.

PERINATAL INTERACTION BETWEEN THE MICROBIOTA AND GUT MACROPHAGES WITH INTEGRATION OF GROUP B STREPTOCOCCI (GBS)

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The main establishment of the intestinal microbiota takes place in the perinatal stage of the neonate. It is a very dynamic process, as its integrating many very different species of bacteria, which are ranging from commensal Bifidobacteria to mucosal pathogens like group B streptococci (GBS). The development of intestinal macrophages (Mϕ) also takes place during this important period of time, especially the transition from embryonic to bone marrow (BM-) derived macrophages (Mϕ). GBS is a well-known cause for live threatening neonatal sepsis and meningitis in infants. Around 50% of the colonized mothers pass on GBS to their newborn, where around 1% develop a neonatal sepsis and meningitis. Factors that steer perinatal development of the intestinal microbiota-immune interface to allow for integration of GBS into the neonatal microbiota but promote resistance against invasive infection remain largely unsolved. Mϕ adaption is influenced by specific bacterial exposure mainly in the described perinatal time period. Especially metabolic programming and epigenetic imprinting in Mϕ are changed in different bacterial conditions. Mϕ adaption and the conditioning of the microbial environment of streptococcal niches are most likely involved in mediating colonization stability of mucosal pathogens. Despite its high medical value and relevance, the crosstalk between macrophages and microbiota and their impact on neonatal development have not been well studied. Our goals are to determine the contribution of maternal versus postnatal microbiota to Mϕ, to delineate key factors driving those interactions and to identify ecosystem members that prevent GBS dissemination. My project is focusing on the impact of GBS on Mϕ in different perinatal time points, Therefore mice were exposed to GBS at p14 and analyzed 2 or 4 days post infection (dpi). Interestingly, I observed activated Mϕ in the small intestine, whereas colonic lamina propia (LP) Mϕ inactivated on a transcriptomic and metabolic level at 2 and 4 dpi. In contrast, colonic monocytes showed an activated phenotype. In the future, we would like to repeat the experiments by using different fate mapping mouse lines to investigate whether the origin of Mϕ is critical. In addition, we aim to expand our analysis and challenge mice with GBS at different timepoints.

USING SYNTHETIC MICROBIAL COMMUNITIES AS A TOOL TO UNDERSTAND MECHANISMS OF STRAIN-STRAIN INTERACTIONS

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The mammalian gut is colonized by a variety of microorganisms such as fungi, bacteria, archaea and viruses. The microbiota provides its host several benefits, e.g. via nutrient supply or protection against invading pathogens. These microbiota functions are dependent on the composition of the inhabiting microbial community and inter- and intraspecies interaction networks. Understanding individual species interactions and their consequences for the mammalian host is hindered by the complexity of the natural gut microbiome. Here, defined microbial model communities such as the Oligo-Mouse-Microbiota (OMM^{12}) can serve as a tool to analyze bacterial ecology in detail by reducing complexity and increasing experimental manipulability.

In recent work we used the OMM^{12} model to study the keystone-species concept in gut microbial communities. For this purpose, single species drop-out communities were constructed and grown in five different media. This approach enabled us to follow changes in community composition and metabolite profiles caused by the absence of every individual community member. It was shown, that bacterial interactions were highly dependent on the nutritional background and that no universal key-species could be identified over all the different growth media. These findings indicate that results on bacterial ecology are context-dependent, which has consequences for the comparability of studies working with different environmental conditions.

In order to translate our results into a human-relevant context, the goal of an additional project is to construct a synthetic bacterial community that mimics the neonatal gut microbiome. For this purpose, selected species are first isolated from neonatal stools and in addition isolates from strain collections are used to obtain a model community that is both taxonomically and functionally representative. This synthetic community will then be established in a bio-fermenter system with different, defined media, allowing the manipulation and the elucidation of strain-strain interactions, which affect community assembly and community function.

INVESTIGATING THE IMPLICIT DIVERSITY OF THE *MORAXELLACEAE* FAMILY USING THE TAXONOMY INFORMED CLUSTERING (TIC) ALGORITHM

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The family *Moraxellaceae*, which includes the genera *Acinetobacter*, *Moraxella*, and *Psychrobacter*, is a diverse group of bacteria with ecological and clinical significance. Some species can cause infections in humans and animals and have emerged as important agents of nosocomial infections. While most members of the family are considered saprophytes of little clinical significance, the study of their diversity is important to understand their potential as pathogens and for the development of treatments as well as its other members for use in industrial applications. In this survey, we applied Taxonomy Informed Clustering (TIC) on above 550,000 sequences, which were assigned to the *Moraxellaceae* family from three sources (IMNGS, SILVA, and LPSN databases) in order to gain insight into the implicit diversity of this bacterial family at genus and species level. The results reveal higher diversity at both levels. The TIC algorithm suggests more than 200 and 20,000 novel clusters at genus and species level, respectively. Considering 172 validly published species of this family, this finding recommends further investigation in this and other families in order to understand microbiological communities.

IDENTIFICATION OF MICROBIOTA-DEPENDENT MECHANISMS GOVERNING AHR-DEPENDENT INFLAMMATION

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Organ damage caused by inflammation is a key pathomechanism in diverse diseases such as chronic kidney disease (CKD), multiple sclerosis (MS), and inflammatory bowel disease (IBD). CKD is a common, progressive disease that results from genetic and environmental risk factors. CKD is often accompanied by diseases common in industrialized countries, e.g., diabetes mellitus and hypertension. Inflammation plays a major role in the progression of CKD causing renal fibrosis, cardiac alterations, and damage to cardiovascular organs. Current treatments are usually applied too late and cannot sufficiently slow CKD-associated inflammation, which frequently ultimately results in kidney failure.

The aryl hydrogen receptor (AhR) is a ligand-activated transcription factor that plays a key role in the dysregulation of the immune system not only in CKD, but also in MS, IBD and specific types of cancer. AhR is expressed in immune and non-immune cells and regulates the expression of several immunomodulatory genes. For instance, AhR drives the differentiation of regulatory T cells as well as the expansion of T helper 17 and 22 cells upon activation. AhR integrates a plethora of different signals derived from the environment, diet, microbiota, or host metabolism. Especially diet- and microbiota-derived tryptophan- and indole-metabolites are activators of the AhR. In CKD, microbiota-derived indoles have been reported to accumulate in the blood due to reduced renal excretion causing sustained activation of the AhR and exacerbating inflammation. An unhealthy, so-called Western diet characterized by high salt and fat intake, is an additional risk factor for CKD.

Since AhR activity and the composition of the gut microbiome can be modulated by diet, it indicates a promising, yet underexplored therapeutic potential. Many studies investigating the effect of diet on the immune system suggest a causative link between diet, gut microbiota, and inflammation. However, the regulatory mechanisms between AhR and microbiota driving inflammation are still unclear. An improved understanding of disease- and cell-specific effects has the potential to facilitate therapeutic approaches via agonistic or antagonistic modulation of AhR. Furthermore, it could provide patients a guideline how they can influence disease progression and inflammation themselves via modulation of dietary behavior. Therefore, the aim is to analyze the role of the AHR as a disease overarching mechanism and the link between AhR activity, microbiota, and inflammation.

CUTANEOUS MICROBIOMES OF HIDRADENITIS SUPPURATIVA AND DARIER' DISEASE SHOW UNIQUE PATTERNS OF MICROBIAL DYSBIOSIS

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The cutaneous microbiome plays essential roles in the maintenance of skin homeostasis. There is increasing evidence that microbial dysbiosis is involved in the pathogenesis of inflammatory skin disorders such as atopic dermatitis and psoriasis. Nevertheless, little is known about microbiome features of less frequent or rare diseases. We investigate here the microbiome of two rare inflammatory skin diseases, namely Hidradenitis suppurativa (HS) and a monogenetic skin disorder known as Darier' disease (DD). Skin swabs were collected from 42 HS patients, 14 DD and healthy matched controls, then analyzed using 16S metabarcoding. Our data show that HS skin is characterized by an expansion of pathogens from the *Peptoniphilus* group, in addition to *Corynebacterium urealyticus* and *Finegoldia magna* at the cost of beneficial commensals, as *Staphylococcus hominis*, *Cutibacterium acnes* and *Staphylococcus epidermidis*. We furthermore investigated the effects on HS microbiome of adalimumab and systemic antibiotics (clindamycin/rifampicin) often prescribed for this disease. In contrast to adalimumab, antibiotic therapy noticeably improved the HS dysbiosis by increasing the microbial richness and the proportion of skin commensals. The profiling of DD skin microbiome revealed a significant loss of microbial diversity and drop of beneficial commensals. The expansion of inflammation-associated microbes as *S. aureus* and *S. warneri* was strongly correlated with disease severity. DD microbiome also exhibited an expansion of taxa associated with body malodor often reported for these patients. DD skin transcriptomics showed marked upregulation of epidermal repair, inflammatory and immune defence pathways reflecting epithelial and immune response mechanisms to DD dysbiosis. An accurate characterization of skin microbiome in rare inflammatory skin disorders would improve our understanding of its role in disease pathogenesis and guide the development of adequate therapies.

Keywords: Hidradenitis suppurativa, Darier's disease, Microbiome, 16S, Dysbiosis, adalimumab**,** clindamycin/rifampicin.

MICROBIAL ENERGY IN IMMUNE HOMEOSTASIS

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The potential contribution of microbial fermented dietary fiber towards a person's total energy intake has been reported to be as high as 10%. However, the impact of this energy on the host's physiology remains poorly understood. In light of this knowledge gap, we have put forth a hypothesis that the energy provided by the microbiota by fermentation of indigestible fiber plays a crucial role in regulating immune cell homeostasis and function.

To test this hypothesis, we have embarked on an in-depth metabolic analysis of germfree mice. Additionally, we have employed flow cytometry to investigate the egress of monocytes from the bone marrow in these mice. Strikingly, we have observed that the egress of monocytes is markedly restricted in germfree mice, akin to the fasting state. Importantly, we have ruled out decreased monocyte differentiation in the bone marrow as the cause of this phenomenon. It is noteworthy that we have also observed similar effects in mice fed a diet consisting of non-fermentable fiber, which provides less microbial energy to the host.

Our findings suggest that not only direct immune signaling or microbial metabolites, but also the energy provided to the host through microbial fermentation, may play a crucial role in immune homeostasis.

HOST FACTORS DRIVING GUT MICROBIOME MATURATION IN EARLY LIFE

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The microbiome-immune system co-development in the infant gut may have consequences on the susceptibility to inflammatory and immune-mediated diseases. Our functional understanding of the initial colonization process within the infant gut, therefore, has a direct impact on our ability to manage and maintain human health. However, while numerous studies have focused on the role of host genetics in shaping the gut microbiome, little is known about the identity and role of (soluble) host factors on gut microbiome establishment and maturation in early life. We therefore aimed to determine the postnatal dynamics of selected soluble host factors and its impact on microbiota composition and function in the neonatal gut. Fecal samples and from 16/133 longitudinally sampled infants (1-2, 4 and 8 weeks, 4, 5, 6, 9, 11 and 14 months) and their mothers (1-2 weeks post-partum) and from 90 cross-sectional infants (8 weeks) were profiled by means of targeted host fecal proteomic approach and whole-metagenome sequencing. Bifidobacteria dominated up to 9 months of age, while *Bacteroides* were abundant at all time points. The facultative aerobes gradually declined from the first weeks of life towards 14 months (*Escherichia* and *Klebsiella*) or rapidly disappeared (*Enterobacter*). On the other hand, some specialists appeared at later time-points as well (*Akkermansia* at 4 months, *Faecalibacterium* at 6 months and *Lachnospiraceae* at 9 months). In addition, despite the large heterogeneity in protein concentrations between infants and over time, we could clearly discriminate formula-fed from breastfed infants.

To understand the dynamics of proteins in the infant gut, we analyzed their associations with the composition and function of gut microbes using metagenomics while accounting for confounders. Our findings revealed that Bacteroides species showed strong positive associations with protein concentrations, while Bifidobacteria showed more negative relationships. We annotated the metagenome-assembled genomes using prodigal and gtdbtk and processed them through GhostKoala to study their taxonomy and proteome. We suggest that the diversity in resistance mechanisms, such as proteolytic degradation, may explain the varying associations observed. To further investigate these associations, we isolated related strains and will examine their differential protein-susceptibility in vitro. Overall, our study provides insight into the interplay between host and microbes in the infant gut.

NFDI4MICROBIOTA: TOWARDS FAIR AND COMPREHENSIVE DATA IN MICROBIOME RESEARCH

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The NFDI4Microbiota consortium [1], a part of the German National research Data Infrastructure (NFDI), aims to support microbiological research by providing a comprehensive platform for data management, analysis, and collaboration. With a strong focus on the FAIR (findable, accessible, interoperable and re-usable) data principles [2], open science, and reproducible research, the consortium strives to boost the cultural shift required to enable sustainable microbiome research.

To achieve this, NFDI4Microbiota generates awareness among researchers about the importance of FAIR principles, open science, and reproducible research, fostering their integration into everyday research practices. Via NFDI4Microbiota's Knowledge Base and comprehensive training programs, the consortium equips the microbiology community with the necessary skills and literacy for efficient and data-driven microbiome research.

To create FAIR research, standardization plays a crucial role. By standardizing data processing, analysis, and metadata collection, the consortium increases the value of data, making it more accessible and interpretable. The utilization of controlled vocabularies and ontologies enables the creation of machine and human-readable datasets and metadata information, facilitating data integration and interoperability. In combination with providing high-quality tools and workflows for FAIR data analysis, this will lead to sustainable scientific advancements both nationally and through international efforts.

The consortium places a strong emphasis on community outreach and contributions to engage with the research community. With diverse Use Cases, NFDI4Microbiota covers a wide range of topics, including multi-omics, data provenance, metadata databases, microbial strain mappings, and benchmarking workflows. In summary, NFDI4Microbiota will serve as a central hub in Germany to support the microbiology community with data access, analysis services, data/metadata standards, and training.

Ref.:
[1] https://nfdi4microbiota.de/;
[2] Wilkinson, M., Dumontier, M., Aalbersberg, I. et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 3, 160018 (2016). https://doi.org/10.1038/sdata.2016.18

EXPLORING THE ROLE OF EVOLUTION IN RESISTANCE AND RESILIENCE OF GUT BACTERIA TO ANTIBIOTICS

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The mammalian gut is a highly dynamic microbial ecosystem that severely impacts health and disease. Throughout the host life span gut bacterial communities are exposed to several factors that challenge its stability and may result in a dysbiotic state which impacts host health. Antibiotics have the potential to alter the composition of the gut microbiota and can therefore disturb microbiome homeostasis. Resistance and resilience are the main driving forces of bacterial community stabilization upon disturbance. Resistance refers to the insensitivity of a community towards disturbance, whereas resilience measures the rate of recovery after disturbance. Resilience and resistance in bacterial communities are influenced by bacterial interactions and their metabolic interchange. Evolution plays a crucial role in shaping metabolic networks between bacterial members and functions of the community. Although there has been extensive research on community composition and function, the impact of community evolution in shaping resistance and resilience remains unknown.

The complexity of the gut microbiota states a considerable challenge when allocating specific attributes to its individual members, emphasizing the need for a more simplistic yet functional model system. The oligo-mouse-microbiota (OMM^{12}) is a synthetic bacterial consortium comprising 12 bacterial isolates from the mouse intestine, which represent fundamental functions of the complex gut, such as short chain fatty acid production and colonization resistance against enteric pathogens. The reduced complexity and functional relevance of the OMM^{12} provide the possibility to longitudinally investigate bacterial evolution and unravel possible metabolic interactions on single strains level.

In this study, we use the OMM^{12} consortium to explore the effects of evolution on bacterial community resistance and resilience to antibiotics. We measure community composition, resistance, and resilience upon pulsed antibiotic treatment before and after community evolution in an *in vitro* batch culture system for 20, 40, 60, and 80 days. This study will broaden our mechanistic understanding of gut microbiota responses towards antibiotic disturbances.

SPEAKERS – KEYNOTE LECTURES & HOT TOPICS

KEYNOTE LECTURES

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1. Louie TJ et al. N Engl J Med 2011;364: 422-431 **2.** Cornely OA et al. J Clin Oncol 2013; 31: 2493–2499 **3.** Fachinformation Dificlir®, Stand März 2021
4. Goldstein EJC et al. Clin Infect Dis 2012; 55 (Suppl 2): 143–148 **5.** Van Prehn J et al. Clin Microbiol Infect 2021; S1198-743X(21)00568-1. DOI: 10.1016/j.cmi.2021.09.038

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