

DEAR PARTICIPANTS!

On behalf of the Volkswagen Foundation I am pleased to welcome you to our Herrenhausen Conference “Beyond the Intestinal Microbiome – From Signatures to Therapy”!

As the largest private research funder in Germany we want to establish our Herrenhausen Conferences as a platform for a lively dialogue on current research questions which translate into social or health-related challenges for society and individuals. Cardiovascular and autoimmune diseases as well as diabetes exert a heavy burden on affected individuals and societies. The WHO estimates that by 2030 more than 23 million people will die every year from cardiovascular diseases alone. Thus, exploring new ways of preventing and curing these severe and chronic diseases poses an exciting research challenge and is also a pressing social topic. As researchers are beginning to understand the fascinating linkages between our organism and our gut microbiota, the latter has emerged as a pivotal player for our overall health. It is also thought to be a novel contributor for diseases including diabetes, Crohn’s disease, and even mental disorders. Thus, defining, exploring and improving our gut health may hold an enormous preventive and curative potential. This Herrenhausen Conference was conceived in order to encourage you to look beyond the state of the art – to think about open research questions that need to be addressed to make best use of our knowledge base, and to move this field of research towards translational medicine.

Dear participants! It is a great pleasure to welcome you to Herrenhausen Palace. We hope you will enjoy fruitful discussions surrounding the opportunities and challenges in microbiome research.

Yours sincerely,

Wilhelm Krull

Secretary General, Volkswagen Foundation

OCTOBER 8-10, 2014

BEYOND THE INTESTINAL MICROBIOME – FROM SIGNATURES TO THERAPY

HERRENHAUSEN CONFERENCE

HERRENHAUSEN PALACE, HANOVER, GERMANY

PROGRAM

WEDNESDAY **OCTOBER 8, 2014**

- 2:00 P.M.** WELCOME ADDRESS
AUDITORIUM **Wilhelm Krull**, Secretary General, Volkswagen Foundation
- 2:15 P.M.** **KEYNOTE**
THE GUT MICROBIOTA IN HEALTH AND DISEASE
Karsten Kristiansen, University of Copenhagen and BGI-Shenzhen
- 3:15 P.M.** COFFEE BREAK
FOYER
- 3:45 P.M.** **FROM MOLECULES TO CELLS**
AUDITORIUM CHAIR **Philip Rosenstiel**, University of Kiel
- LINKING PATHOGEN VIRULENCE, THE MICROBIOTA AND DISEASE
Gabriel Nunez, University of Michigan
- COPING WITH STRESS IN THE INTESTINAL CRYPT
Arthur Kaser, University of Cambridge
- PERMISSIVE SIGNALS FROM THE COMMENSAL MICROBIOTA
POISE EXPRESSION OF PROINFLAMMATORY CYTOKINE GENES
IN MONONUCLEAR PHAGOCYTES
Andreas Diefenbach, University of Mainz Medical Centre

All academic titles have been omitted.

5:30 P.M. LIGHTNING TALKS I

6:00 P.M. POSTER SESSION AND APERITIF
FOYER

7:00 P.M. MUSICIAN'S SYMBIOSIS
FESTSAAL **Noé Inui** (Violin) & **Vassillis Varvaresos** (Piano)
www.noeinui.com
www.varvaresos.com

7:45 P.M. CONFERENCE DINNER

THURSDAY **OCTOBER 9, 2014**

9:00 A.M. CELLS – ATTACK AND DEFENSE
AUDITORIUM CHAIR **Julia-Stefanie Frick**, University of Tuebingen

RECIPROCAL INTERACTIONS BETWEEN THE INTESTINAL MICROBIOTA
AND MUCOSAL ANTIBODIES

Oliver Pabst, RWTH Aachen University Medical Clinic

MICROBIOTA-MEDIATED DEFENSE AGAINST INTESTINAL INFECTION
Eric G. Pamer, Memorial Sloan-Kettering Cancer Center

10:10 A.M. COFFEE BREAK AND POSTER SESSION
FOYER

10:40 A.M. COMPROMISED MUCOSAL ANTIMICROBIAL DEFENSE AS A DRIVER
OF CHRONIC INTESTINAL INFLAMMATION
AUDITORIUM **Jan Wehkamp**, University Hospital Tübingen

GENETICALLY MODIFIED LACTOCOCCUS LACTIS FOR PRECISION
INTERVENTION IN THE GI TRACT
Lothar Steidler, ActoGeniX NV

11:50 A.M. LIGHTNING TALKS II

12:15 P.M. POSTER SESSION AND LUNCH
FOYER

2:00 P.M. KEYNOTE

AUDITORIUM GAMES BETWEEN MICROBES WITH RULES SET BY THE HOST?
Arne Traulsen, Max Planck Institute for Evolutionary Biology

2:45 P.M. FROM CELLS TO NETWORKS / ECOSYSTEMS

CHAIR **Dirk Haller**, Technical University of Munich

EXPLOITING NATURE'S TOOLKIT: MODEL SYSTEMS OF SYMBIOSIS
Margaret McFall-Ngai, University of Wisconsin-Madison

REGULATION OF GUT MICROBIOTA BY FOXP3 AND IGA
Sidonia Fagarasan, Riken Center for Integrative Medical Sciences

4:00 P.M. COFFEE BREAK

FOYER

4:45 P.M. TARGETING THE HUMAN SMALL INTESTINE AND THE IMPACT OF PROBIOTICS

AUDITORIUM **Michiel Kleerebezem**, NIZO food research and Wageningen University

DIET, GUT MICROBIOTA AND WESTERN LIFESTYLE DISEASES
Charles R. Mackay, Monash University

6:00 P.M. DINNER

FESTSAAL

7:00 P.M. PUBLIC EVENT

AUDITORIUM (in German, conference attendees are welcome)
HUNDERT BILLIONEN MITBEWOHNER –
WIE MIKROORGANISMEN UNSERE GESUNDHEIT BEEINFLUSSEN
Dirk Haller, Technical University of Munich
Harald Renz, University of Marburg
Mathias Hornef, Medical School Hanover
Kerstin Berer, Max Planck Institute of Neurobiology
HOST **Daniel Lingenhöhl**, spektrum online

FRIDAY **OCTOBER 10, 2014**

9:00 A.M. FROM NETWORKS TO ORGANISMS

AUDITORIUM CHAIR **Hartmut Wekerle**, Max Planck Institute of Neurobiology

GENDER BIAS IN AUTOIMMUNITY:
UNDER CONTROL OF HORMONES AND MICROBES
Alexander Chervonsky, University of Chicago

AUTOIMMUNITY IN THE BRAIN – THE ROLE OF THE GUT-BRAIN AXIS
Gurumoorthy Krishnamoorthy, Max Planck Institute of Neurobiology

10:10 A.M. LIGHTNING TALKS III

10:40 A.M. COFFEE BREAK AND POSTER SESSION

FOYER

11:40 A.M. FROM "BENCH TO BEDSIDE"

AUDITORIUM CHAIR **Stephan C. Bischoff**, University of Hohenheim

ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS OF DIABETES
Fredrik Bäckhed, University of Gothenburg

ENVIRONMENTAL MICROBES IN THE HYGIENE HYPOTHESIS
Harald Renz, University of Marburg

MINING FOR NOVEL THERAPEUTIC BACTERIAL STRAINS AGAINST
HUMAN DISEASE USING FECAL TRANSPLANTATION
Max Nieuwdorp, AMC Amsterdam and University of Gothenburg

1:20 P.M. LUNCH BREAK

FOYER

2:10 P.M. CLOSING TALK

AUDITORIUM TWIN MICROBIOMES REVEAL A HUMAN GENETIC INFLUENCE
ON THE COMPOSITION OF THE GUT MICROBIOME WITH
CONSEQUENCES FOR HEALTH
Ruth E. Ley, Cornell University

3:00 P.M. END OF CONFERENCE

SPEAKERS

FREDRIK BÄCKHED
ALEXANDER CHERVONSKY
ANDREAS DIEFENBACH
SIDONA FAGARASAN
ARTHUR KASER
MICHIEL KLEEREBEZEM
GURUMOORTHY KRISHNAMOORTHY
KARSTEN KRISTIANSEN

RUTH E. LEY
CHARLES R. MACKAY
MARGARET MCFALL-NGAI
MAX NIEUWDORP
GABRIEL NUÑEZ
OLIVER PABST
ERIC G. PAMER
HARALD RENZ
LOTHAR STEIDLER
ARNE TRAUlsen
JAN WEHKAMP

PROGRAM COMMITTEE AND CHAIRS

STEPHAN C. BISCHOFF
JULIA-STEFANIE FRICK
DIRK HALLER
PHILIP ROSENSTIEL
HARTMUT WEKERLE

FREDRIK BÄCKHED

UNIVERSITY OF GOTHENBURG

Professor Fredrik Bäckhed combines clinical oriented research with gnotobiotic mouse models to address the role of the normal gut microbiota in metabolic diseases. He holds a Ph.D. from Karolinska Institutet, Sweden and performed his postdoctoral training at Washington University, St Louis. Dr. Bäckhed is a professor at the University of Gothenburg, Director of the Wallenberg Laboratory for cardiovascular research, and co-director of the Center for Cardiovascular and Metabolic Research. In 2011 he was appointed Professor at the University of Copenhagen. Dr. Bäckhed has co-authored 60 research papers in international peer-reviewed journals, many of which are in high-impact journals such as *Nature*, *Science*, *Cell*, and *Proceedings of National Academy of Sciences* and he has received numerous awards.

ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS OF DIABETES

The human gut is inhabited by trillions of bacteria, gut microbiota, that have co-evolved with us and have an effect on our physiology within and outside the gut. Our bodies are exposed to an immense number of bacteria at birth but it is relatively unclear how the gut microbiota becomes established and how the feeding pattern affects the microbial ecology. The gut microbiota has recently been suggested as a novel contributor to obesity and related comorbidities, such as type 2 diabetes (T2D) and cardiovascular diseases (CVD). We recently found that the gut microbiota is altered in patients with CVD and T2D and that we can classify patients and T2D patients based on the microbiota. Using germ-free mice we have causally linked the gut microbiota to obesity and insulin resistance, and have recently found that the gut microbiota modulates adipose inflammation, bile acid signaling, and enteroendocrine cell function. During the past years it has become clear that bariatric surgery modulates gut microbial ecology. However, it is unclear whether the altered gut microbiota directly contributes to the improved metabolic outcome of bariatric surgery. The aim of my talk is to discuss how the gut microbiota is established early in life and how a perturbed microbiota may contribute to metabolic disease later in life.

ALEXANDER CHERVONSKY

UNIVERSITY OF CHICAGO

Alexander Chervonsky is a professor in the Department of Pathology, and Chair of the Committee on Immunology at the University of Chicago. He received his M.D. from the 1st Moscow State Medical School, and his Ph.D. from the Cancer Research Center in Moscow, Russia. He did his postdoctoral training at Yale University, where he continued working as an Associate Research Scientist in the Section of Immunobiology from 1993 to 1997 before moving to the Jackson Laboratory in Bar Harbor, Maine. After working there as an Associate Staff Scientist until 2003 and as Staff Scientist until 2005 he became an Associate Professor at the University of Chicago's Department of Pathology. Since 2013 he has held a professorship in the Department of Pathology.

GENDER BIAS IN AUTOIMMUNITY: UNDER CONTROL OF HORMONES AND MICROBES

Gender bias and the role of sex hormones in autoimmune diseases are well established. In specific-pathogen-free (SPF) non-obese diabetic (NOD) mice, females have a 1.3-4.4 times higher incidence of type 1 diabetes (T1D). Germ-free (GF) mice lose the gender bias (female/male ratio 1.1-1.2). Gut microbiota differed in males and females, a trend reversed by male castration. Some male-dominant microbes protected GF males upon transfer, although protection did not correlate with androgen levels. Gene expression analysis suggested pathways and mechanisms involved in the protection of males from T1D by microbiota. Thus, androgens and microbes work together to provide protection, whereas hormone-supported selective microbial variation may work as a positive feedback mechanism contributing to the gender bias of autoimmune diseases. Androgen-mediated gene expression and its regulation by microbes has broad implications in autoimmunity.

ANDREAS DIEFENBACH

UNIVERSITY OF MAINZ MEDICAL CENTRE

Andreas Diefenbach is Professor and Chair of Medical Microbiology at the University of Mainz. He graduated in Microbiology and Immunology from the University of Erlangen and obtained postdoctoral training at the Department of Molecular and Cellular Biology, University of California, Berkeley. Prior to joining the University of Mainz, he was an Assistant Professor at the Skirball Institute of Biomolecular Medicine, New York University, and a Full Professor at the University of Freiburg. His current research interests include the transcriptional circuitry that control fate decisions of innate lymphoid cells and their adaptation by environmental factors (microbiota, nutrients). As a Physician Scientist, Andreas won grant support from the *Howard Hughes Medical Institute* and from the *European Research Council*. He was awarded the Main Scientific Prize of the *German Society of Hygiene and Microbiology*.

PERMISSIVE SIGNALS FROM THE COMMENSAL MICROBIOTA POISE EXPRESSION OF PROINFLAMMATORY CYTOKINE GENES IN MONONUCLEAR PHAGOCYTES

The commensal microbiota has a profound impact on the development and function of immune cells at mucosal sites. Recently, we found that mononuclear phagocytes throughout the body, including those residing in non-mucosal lymphoid organs of germ-free mice, failed to produce proinflammatory cytokines in response to microbial stimulation. Using genome-wide transcriptional profiling, we now demonstrate that pathogen-inducibile expression of a set of inflammatory response genes, including the various type I interferon genes, required poising by signals from the commensal microbiota. Our data reveal a previously unrecognized role for postnatally colonizing microbiota in the introduction of chromatin level changes in the mononuclear phagocyte system, thereby poising expression of central inflammatory genes to initiate a powerful systemic immune response during viral infection.

SIDONA FAGARASAN

RIKEN CENTER FOR INTEGRATIVE MEDICAL SCIENCES (IMS)

Sidonia Fagarasan's research addresses the symbiotic relationships between gut bacteria and the immune system. She holds an M.D. degree from University of Medicine and Pharmacy, Cluj, Romania and a Ph.D. degree from Kyoto University. Currently a team leader at the RIKEN Center for Integrative Medical Sciences, Yokohama Japan, she has co-authored more than 50 research papers in international peer-reviewed journals, many of which are in high-impact journals such as Science, Immunity, Nature, Cell, and Proceedings of National Academy of Sciences, and she has received numerous awards.

REGULATION OF GUT MICROBIOTA BY FOXP3 AND IGA

The main function of the immune system is to protect the host against pathogens such as bacteria or viruses. However, unlike the systemic immune system, the gut immune system does not eliminate microorganisms but instead nourishes rich bacterial communities and establishes advanced symbiotic relationships. Not only that the gut bacteria are essential for nutrient processing, production of vitamins, and protection against pathogens (through competition for space and nutrients) but the development and maturation of the immune system depends on these bacteria.

Our previous studies demonstrated that the absence of immunoglobulin A (IgA) (the major effector molecule of the adaptive immunity in the gut), or the impaired IgA selection in germinal centers (GC) due to deregulated T cell control, severely affects the balance of gut bacterial communities, resulting in massive activation of the whole body immune system. Together, the results point to an important role played by the adaptive immune system in regulating the microbial communities in the gut. I will discuss our most recent findings of how the adaptive immune system mediates host-microbial symbiosis by controlling the diversification and balance of bacterial communities required for gut homeostasis and health.

ARTHUR KASER

UNIVERSITY OF CAMBRIDGE

Arthur's scientific interest centers on the intestinal epithelium at the interface of the microbiota and host with its ancient role as an innate immune compartment that has evolved to pervasively orchestrate the mucosal immune response. His laboratory has a particular interest in inflammatory bowel disease and the genetically affected pathways that are involved in interaction with the environment that contribute to its pathogenesis. Arthur graduated from Leopold Franzens University of Innsbruck, Austria, and did post-doctoral work in Innsbruck and at Harvard Medical School. He holds the University Chair in Gastroenterology at the University of Cambridge and is Honorary Consultant Physician at Cambridge University Hospitals – Addenbrooke's Hospital.

COPING WITH STRESS IN THE INTESTINAL CRYPT

Autophagy and the unfolded protein response are tightly linked in a cross-compensatory fashion within specialized intestinal epithelial Paneth cells at the base of intestinal crypts. These cells provide the niche for intestinal stem cells, produce inflammatory mediators, and secrete antimicrobial peptides, altogether critical elements for the orchestration of host – microbial mutualism at the intestinal mucosal surface. A 'conditionally' hypomorphic genetic variant of *ATG16L1* is one of the strongest genetic risk factor of Crohn's disease, and genetic deletion of *Atg16l1* in the murine intestinal epithelium in the presence of impaired unfolded protein response function originates a disease that phenocopies Crohn's disease. We will discuss host and microbial mechanisms and their reciprocal consequences under homeostatic and pathological conditions and implications for our understanding of chronic inflammation and its consequences in the intestinal tract.

MICHIEL KLEEREBEZEM

NIZO FOOD RESEARCH AND WAGENINGEN UNIVERSITY

Michiel Kleerebezem is employed at NIZO food research and Wageningen University, where he holds a professorship in the Host Microbe Interactomics Group. He participates in the TI Food & Nutrition consortium, where he was appointed as scientific director in 2011. He is specialized in the molecular biology of lactic acid bacteria, and intestinal microbes in relation to their interaction with the human host. He has (co-) authored more than 200 peer-reviewed publications and has submitted more than 25 patent applications.

TARGETING THE HUMAN SMALL INTESTINE AND THE IMPACT OF PROBIOTICS

Most of the efforts to study the human intestine microbiota have focused on the large intestine or fecal microbiota. To date, the microbiota of the small intestine is much less studied due to its poor accessibility in healthy volunteers. This presents an important hiatus in our understanding of the role of the microbiota in human health, since in this part of the intestine (i) first encounters of microbiota and dietary components take place, and (ii) the mucosa plays a profound role in immune and metabolic health of the host. Therefore, it is important to characterize the normal microbiota of the human small intestine and its capacity to modulate mucosal and systemic host physiology. This presentation will focus on the characterisation of the small intestinal microbiota in humans. In addition, it will show how probiotic consumption drastically modulates the small intestine microbial ecosystem, and elicits specific molecular responses in the mucosal tissues that can be connected to physiologically relevant outcomes. The presentation will also highlight the pursuit of the bacterial effector molecules that drive the mucosal responses. Finally, the findings presented will be placed into a context of human individuality and the concept of 'the bandwidth of health', which questions the applicability of probiotics in the general public and favours their application in stratified subpopulations.

GURUMOORTHY KRISHNAMOORTHY

MAX PLANCK INSTITUTE OF NEUROBIOLOGY

Gurumoorthy Krishnamoorthy studied pharmacology at the National Institute of Pharmaceutical Education and Research, India. He was then trained at the Max Planck Institute of Neurobiology and received his Ph.D. in 2007 from Ludwig Maximilians Universität Munich. After a brief postdoctoral period (2007-2008), he was appointed to his current position as a project leader at the Max Planck Institute of Neurobiology in the Department of Neuroimmunology, Germany. He received the Sobek prize from the German MS society in 2009. His research interests are to investigate the molecular mechanisms of the initiation and regulation of CNS autoimmunity. Gurumoorthy Krishnamoorthy's current work focuses on the role of gut microbiota in CNS autoimmunity.

AUTOIMMUNITY IN THE BRAIN: THE ROLE OF THE GUT-BRAIN AXIS

Multiple Sclerosis (MS), an autoimmune demyelinating disease affecting the central nervous system (CNS), causes tremendous disability in young adults and inflicts a huge economic burden on society. The development of MS is determined by both genetic and environmental factors. The incidence of MS is steadily increasing in many countries, arguing for environmental factors driving changes in disease induction. Emerging evidence, particularly in the animal models of MS, implicate gut microbiota in triggering CNS autoimmunity. However, precisely how and which gut microbial species are involved in triggering processes is still unknown. Moreover, whether gut microbiota is important in MS patients is still unclear. Microbial organisms may trigger the activation of CNS-specific auto-aggressive lymphocytes either through molecular mimicry or via bystander activation. The purpose of the presentation is to critically evaluate the role of gut microbiota in mouse models of MS. This presentation will also highlight the approaches we are taking to translate these findings to MS patients.

KARSTEN KRISTIANSEN

UNIVERSITY OF COPENHAGEN AND BGI-SHENZHEN

Karsten Kristiansen is Professor of Molecular Biology and Head of the Department of Biology, University of Copenhagen, and also professor at BGI-Shenzhen. Professor Kristiansen is member of the Danish Academy of Natural Sciences. He currently heads a research group comprising 9 postdocs and 18 doctorate students. His research focuses on metagenomics, genomics, and the regulation of gene expression and cellular differentiation with particular emphasis on energy metabolism and glucose homeostasis.

THE GUT MICROBIOTA IN HEALTH AND DISEASE

The importance of the gut microbiota for regulation of metabolism and immune functions is well established, and evidence has been presented that the gut microbiota may also affect behavior. However, the exact molecular mechanisms by which bacteria in the gut exert their actions still remain elusive. Our laboratory is involved in large-scale metagenomics projects in collaboration with BGI-Shenzhen, using high throughput Illumina-based sequencing of total fecal DNA. These studies have primarily been focused on humans and mice, but have now been extended to encompass several other species including pigs and fish. In this lecture I will first summarize our data on the mouse, the pig, and the human gut microbiota, pointing to differences and similarities. In large scale studies of human cohorts we have recently described changes in the gut microbiota that characterize obese individuals, individuals with type 2 diabetes, and patients suffering from colorectal cancer revealing characteristic changes in the diversity and functional competences of the gut microbiota. I will conclude the lecture by discussing possible functional consequences and perspectives of these findings.

RUTH E. LEY

CORNELL UNIVERSITY

Ruth E. Ley, Ph.D., is an Associate Professor of Molecular Biology and Genetics at Cornell University in Ithaca, NY. She received a Ph.D. from the University of Colorado, Boulder, where she worked with Dr. Steve Schmidt (Ph.D.). Her post doctoral research was with Dr. Norman Pace at the University of Colorado and later with Dr. Jeffrey Gordon at Washington University School of Medicine. Dr. Ley's awards have included the Hartwell Investigator Award, the Arnold and Mabel Beckman Young Investigator Award, a David and Lucile Packard Foundation Fellowship, and an NIH Director's New Innovator Award.

TWIN MICROBIOMES REVEAL A HUMAN GENETIC INFLUENCE ON THE COMPOSITION OF THE GUT MICROBIOME WITH CONSEQUENCES FOR HEALTH

Host interactions with the microbiome are deeply implicated in modern metabolic plagues: metabolic syndrome, type 2 diabetes, and obesity. If we could better understand how the microbiome impacts host metabolism, we could address therapeutically an underlying driver of the biggest health problems that we face today. Eukaryotic species have harnessed the microbiota to extend their phenotypes, yet gut microbiomes are immensely complex. The role of host genetic variation in shaping the microbiome remains to be discerned. Previous work using next-generation sequencing of twin microbiomes has not supported an influence of host genotype on the gut microbiome. However, these studies were likely too under-powered to detect a host genetic effect. From a study of >500 twin pairs, we have recent evidence that human genetic variation is related to variation in the gut microbiome, and that microbes under host genetic influence can be beneficial to the host.

CHARLES R. MACKAY

MONASH UNIVERSITY

Charles Mackay did his Ph.D. at Melbourne University, and worked at the Basel Institute for Immunology, LeukoSite Inc. and Millennium Therapeutics in Boston and Garvan Institute in Sydney, before moving to Monash University in mid 2009. He holds the Chair for Diabetes at Charles Perkins Center, University of Sydney. Mackay's recent work has uncovered molecules and receptors responsible for gut homeostasis. He is a chief proponent of a 'diet hypothesis' to explain the increased incidence of inflammatory diseases in western countries.

DIET, GUT MICROBIOTA, AND WESTERN LIFESTYLE DISEASES

Human disease is affected by diet, as well as by the composition of the gut microbiota, through poorly understood mechanisms. One of the major activities of commensal microbes is digestion of dietary fibre to yield short chain fatty acids (SCFAs). Deficiency of dietary fibre, in particular, has been associated with increased mortality due to various diseases. Decreasing amounts of fibre intake in western countries is one hypothesis for the increased incidences of certain inflammatory diseases. SCFAs affect numerous biological systems, either through stimulation of 'metabolite-sensing' G-protein coupled receptors or through inhibition of histone deacetylases (HDACs). We found that diets deficient in fibre produced marked alterations in the composition of the gut microbiota in mice, and led to exacerbated disease in models of intestinal injury and inflammation, colon cancer, type 1 diabetes, asthma, and wound healing. In contrast, very high intake of dietary fibre protected against these conditions. The burning questions in the field of dietary metabolites to be addressed in future studies are: What is the relative importance of metabolite-sensing GPCRs versus HDACs for gut health and human disease? How important are metabolites such as SCFAs for a 'developmental origin' of disease, i.e. diseases that are put in train in utero or during breast feeding, and which may have an epigenetic basis? What are all the metabolites of beneficial bacteria, and are non-bacterially produced metabolites important as well?

MARGARET MCFALL-NGAI

UNIVERSITY OF WISCONSIN-MADISON

Dr. Margaret McFall-Ngai is a professor in the Department of Medical Microbiology and Immunology, School of Medicine and Public Health, and member of the Symbiosis Cluster group, University of Wisconsin-Madison. Her laboratory studies the role of beneficial bacteria in health using the squid-vibrio model. In addition, she has been heavily involved in promoting microbiology as the cornerstone of the field of biology. She serves on the board of advisors for the Global Health Initiative at the Ecole Polytechnique Federale de Lausanne, Switzerland, and the Forum for Microbial Threats, National Academy of Sciences, USA. She is a member of the American Academy of Arts and Sciences and the National Academy of Sciences, USA.

EXPLOITING NATURE'S TOOLKIT: MODEL SYSTEMS OF SYMBIOSIS

The application of new genomic methods over the last decade has revealed that the most prevalent symbiotic relationships are the essential coevolved partnerships that animals have with beneficial bacteria or mutualistic symbionts. The majority of such associations share a set of common characteristics: they are established anew each host generation, remain stable throughout the host's lifetime, and occur as interactions at the apical surfaces of epithelial cells along the mucosal surfaces. These new findings afforded by advances in biotechnology beg the questions: (i) How do animals initially recognize their appropriate partners, and (ii) how do they maintain them in balance? Biologists are taking a variety of approaches to address these questions. Because in humans and other vertebrates these alliances involve hundreds to thousands of microbial species, several invertebrate associations, which typically have much simpler symbiont communities, are being exploited as natural experimental models. In much the same way as the fruit fly and worm have been used to establish basic principles of developmental biology, these invertebrate symbioses provide a window into the conserved mechanisms underlying interspecies co-existence and communication. This presentation will consider model-system development for future research efforts in the study of host-microbe interactions.

MAX NIEUWDORP

ACADEMIC MEDICAL CENTER (UNIVERSITY OF AMSTERDAM) AND
GOTHENBURG UNIVERSITY

After a residency in Internal Medicine and fellowship in Endocrinology at the AMC-UvA and a postdoctoral fellowship on glycobiology at UC San Diego (Prof. Jeff Esko, department of Cellular and Molecular Medicine), Dr. Nieuwdorp started his own translational research group focusing on translational research aimed at dissecting the causal role of (small) intestinal bacterial strains to reverse insulin resistance, adipose tissue inflammation, and cardiovascular disease.

MINING FOR NOVEL THERAPEUTIC BACTERIAL STRAINS AGAINST HUMAN DISEASE USING FECAL TRANSPLANTATION

Alterations in (small) intestinal microbiota are associated with obesity and insulin resistance, with the latter usually characterized by low grade endotoxemia. We recently showed that fecal transplantation (infusing intestinal microbiota from lean donors) in male recipients with metabolic syndrome has beneficial effects on the recipients' microbiota composition and glucose metabolism via lowering plasma endotoxin levels (Vrieze, Gastroenterology 2012). Moreover, preliminary data suggest that 4 weeks daily oral gavage with one of the identified small intestinal bacterial strains (butyrate producer *Eubacterium hallii*) has dose-dependent beneficial effects on insulin sensitivity and liversteatosis in male db/db mice. Combined, our data suggest that specific intestinal bacterial strains might be developed as therapeutic targets to normalize inflammatory tone and insulin sensitivity in humans. The following challenges remain: According to Koch's postulates for infectious disease, causality instead of association remains to be established for specific intestinal bacterial strains in human disease. Second, a major challenge is currently to establish the relative distribution and relation between proximal (small intestinal) and distal (fecal) gutmicrobiota composition in different disease states associated with altered gutmicrobiota composition. As small intestinal samples are relatively hard to sample, it will be a challenge to establish this relation in different (metabolic) disease states.

GABRIEL NUÑEZ

UNIVERSITY OF MICHIGAN, ANN ARBOR

Gabriel Nuñez earned his M.D. from the University of Seville, Spain. He was trained at the University of Texas Southwestern Medical Center, Dallas (1979-1984) and at Washington University in St Louis (1985-1990). In 1991, he joined the Department of Pathology at the University of Michigan in Ann Arbor, where he now holds the Paul de Kruif Endowed Professorship in Academic Pathology. His laboratory is interested in microbial-host interactions and the role of the microbiota in host defense and inflammatory disease.

LINKING PATHOGEN VIRULENCE, THE MICROBIOTA AND DISEASE

The mechanisms that allow pathogens to colonize the intestine and the indigenous microbiota to inhibit this remain unclear. Previous work has suggested that the microbiota antagonize pathogens through direct competition and via commensal-induced immune responses that restrict pathogen growth. In order to understand the role of the microbiota in controlling pathogen colonization, we have focused our studies on *Citrobacter rodentium*, a model for human infections by attaching/effacing (A/E) bacteria. Unlike normal mice, germ-free animals are unable to eradicate *C. rodentium* from the intestine. The genome of A/E pathogens harbors the locus of enterocyte effacement (LEE) that is critical for bacterial colonization. Early in infection, LEE virulence genes were expressed and required for pathogen growth in conventionally raised, but not germ-free, mice. LEE virulence was down-regulated during the late phase of infection, which led to relocation of the pathogen to the intestinal lumen where it was out-competed by commensals determined, at least in part, by the capacity of the pathogen and commensals to grow on structurally similar carbohydrates. We also found that the host immune system regulates pathogen virulence and acts cooperatively with the microbiota to control pathogen eradication. I will discuss the relevance of our findings for the design of therapeutic approaches to inhibit pathogen colonization using the microbiota.

OLIVER PABST

RWTH AACHEN UNIVERSITY MEDICAL CENTER

The Pabst lab is working to understand the balancing of immunity and tolerance in mucosal tissues. Current projects concentrate on pathways of IgA induction, the regulation of immune responses to food antigen, and immune cell migration. Oliver Pabst studied Biotechnology and obtained his Ph.D. in the field of Developmental Biology. He then focused on Immunology and became a Professor of Mucosal Immunology at Hanover Medical School, Germany before he took on the position as head of the Institute of Molecular Medicine at the RWTH University, Aachen, Germany.

RECIPROCAL INTERACTIONS BETWEEN THE INTESTINAL MICROBIOTA AND MUCOSAL ANTIBODIES

Production of immunoglobulin (Ig) A antibodies is a hallmark host-microbe interaction in the gut. IgA induction is supported by different anatomical sites as well as by various T cell-dependent and T cell-independent processes. However, the contribution of distinct pathways to the overall IgA response remains uncertain. Thus, it is currently not clear how we might best exploit the IgA system in prophylactic vaccination and therapy. We are using next-generation-sequencing to study microbiota-triggered IgA responses in the intestine. Our results suggest that in humans and mice antibody responses to the microbiota largely rely on the diversification of memory B cells. Consistently, the clonal composition of the IgA repertoire is preserved despite major changes in the microbiota during antibiotic treatment. Moreover, the gut IgA repertoire was mirrored by memory B cells and the IgA repertoire in mammary glands of lactating mice. Our findings offer an explanation of how antibody responses are regulated to establish symbiotic host-microbe interactions and how maternal antibodies are optimised throughout life to protect the newborn.

ERIC G. PAMER

MEMORIAL SLOAN-KETTERING CANCER CENTER

Eric G. Pamer received his M.D. degree from Case Western Reserve University Medical School and completed clinical training in Internal Medicine and Infectious Diseases at UCSD Medical Center. He was a postdoctoral fellow with Charles E. Davis at UCSD, Maggie So at Scripps Research Institute, and Michael Bevan at the University of Washington before moving to Yale University. In 2000 he moved his laboratory to Memorial Sloan-Kettering Cancer Center in New York, where he has been Chief of Infectious Diseases and, more recently, Head of the Division of General Medicine.

MICROBIOTA-MEDIATED DEFENSE AGAINST INTESTINAL INFECTION

Infections caused by antibiotic-resistant bacteria generally begin with the colonization of mucosal surfaces, in particular the intestinal epithelium. The intestinal microbiota provides resistance to infection with highly antibiotic-resistant bacteria, including Vancomycin Resistant Enterococcus (VRE) and *Clostridium difficile*, the major cause of hospitalization-associated diarrhea. Metagenomic sequencing of the murine and human microbiota following treatment with different antibiotics is beginning to identify bacterial taxa that are associated with resistance to VRE and *C. difficile* infection. We demonstrate that reintroduction of a diverse intestinal microbiota to densely VRE colonized mice eliminates VRE from the intestinal tract. While oxygen-tolerant members of the microbiota are ineffective at eliminating VRE, administration of obligate anaerobic commensal bacteria to mice results in a billion-fold reduction in the density of intestinal VRE colonization. Our studies indicate that obligate anaerobic bacteria enable clearance of intestinal VRE colonization and may provide novel approaches to prevent the spread of highly antibiotic-resistant bacteria.

HARALD RENZ

UNIVERSITY OF MARBURG

Prof. Harald Renz is director and chairman of the Institute of Laboratory Medicine and Pathobiochemistry of the Philipps-University Marburg, Germany. He is currently the President of the German Society of Allergology and Clinical Immunology. He coordinates the inter-regional Research Consortium of Allergies and Asthma, and serves as vice-speaker of the Universities of Giessen and Marburg Lung Center. His research interest is the pathogenesis of allergies and asthma.

ENVIRONMENTAL MICROBES IN THE HYGIENE HYPOTHESIS

Overwhelming evidence indicates a strong impact of environmental microbes on the programming and the development of (early) immune responses. Based on clinical and epidemiological data, a certain exposure of environmental microbes – particularly of bacteria – seems to be an important pre-requisite for programming immune responses towards the tolerance default program. Such programming on the level of the adaptive immune responses is necessary, and required in order to prevent unwanted (chronic) inflammatory diseases and many autoimmune diseases. The grand challenge is to define the appropriate microbial environment on the cellular and molecular level in order to delineate the underlying mechanism of microbe-host interaction. Microbial diversity is one important finding the scientific community largely agrees upon. Conversely, reduced diversity is closely linked to several clinical phenotypes that precede the clinical onset of the disease, suggesting a cause-effect relationship. This concept implies the loss of evolutionary co-evolved microbial strains and is the result of changes in lifestyle condition. The great challenge is to delineate the molecular pathomechanism of gene-environment interactions and the impact of microbial communities on this complex and intimate relationship. Therefore, it is urgently needed to move this research field towards translational activities.

LOTHAR STEIDLER

ACTOGENIX NV

Lothar Steidler is co-founder of ActoGeniX, where his department engineers novel recombinant *Lactococcus lactis*, designed for in vivo production of therapeutic proteins (cytokines, peptides, allergens). He has assisted in providing regulatory (clinical as well as environmental) documents for several authorities (US, CA, SE, NL, BE). His expertise extends especially to the field of using live, genetically modified microbiota as therapeutics, GMP production and environmental impact assessment of such organisms within the context of clinical trials. Lothar Steidler is a molecular microbiologist (Ghent University, PhD 1995). He invented and pioneered “TopAct” technology (www.actogenix.com/technology; Science, Steidler et al. 2000; 289:1352-1355): the use of recombinant microbiota for topical and active delivery of proteins. A robust environmental containment system (Nature Biotechnology, Steidler et al. 2003; 21:785-789) enabled advance into the first clinical studies ever, using genetically modified microorganisms as therapeutics.

GENETICALLY MODIFIED LACTOCOCCUS LACTIS FOR PRECISION INTERVENTION IN THE GI TRACT

There is a clear deficit in translating microbiome research towards medical applications. Filling this gap represents a genuine challenge to the community. ActoGeniX is at the forefront in performing clinical research with live GM bacteria - ActoBiotics™ - for topical and active (TopAct™) protein delivery (hTFF1, anti-TNF, IL-10, auto-antigens). TopAct™ can greatly add to the field by its inherent capacity to deliver high-end therapeutics. It can harvest potential therapeutics from the microflora as well as target components thereof. High throughput methodology can be applied to visualize deeper understanding of functionalities within the microbiota. This may in an elegant way combine the acquisition of fundamental understanding and translation thereof.

ARNE TRAUlsen

MAX PLANCK INSTITUTE FOR EVOLUTIONARY BIOLOGY

Arne Traulsen (born 1975) studied geophysics and physics in Kiel, Leipzig and Gothenburg. He finished his Diplom in theoretical physics at Leipzig University on spatiotemporal stochastic processes in 2002 and obtained his Ph.D. in theoretical physics at the University of Kiel in 2005, focusing on the connection between statistical physics and evolutionary game theory. With a scholarship from the National Academy of Sciences Leopoldina, he continued as a PostDoc Researcher at Harvard University, where he worked with Martin Nowak on the Program for Evolutionary Dynamics, shifting his focus towards Biology. Since 2007, he has been working at the Max Planck Institute for Evolutionary Biology. From 2008-2013, his group was funded by an Emmy-Noether fellowship of the German Research Foundation, from 2010-2014 he was an independent research group leader funded by the Max Planck Society. In 2012, he became an Honorary Professor for Mathematical Biology at the University Lübeck. In 2014, he was appointed as a director of a new department of evolutionary theory.

GAMES BETWEEN MICROBES WITH RULES SET BY THE HOST?

Evolutionary game theory provides a powerful way to think about interactions between different phenotypes. This mathematical approach allows us to make very general statements about the stability of communities, and is particularly powerful for analyzing the interplay of competition and cooperation and the emergence of polymorphisms. Can this theory be applied to microbial communities in the gut? A combination of simple models and experimental data shows that some general statements about the dynamics in such communities can be made, but a bottom up approach based on transparent mathematical models requires a different view on the data, and in some cases laborious experiments.

JAN WEHKAMP

UNIVERSITY HOSPITAL TÜBINGEN

Prof. Dr. Jan Wehkamp studied Medicine in Lübeck. Following several research stays in the USA and Germany as a student, post-doc, and later as a faculty member of the University of California, he returned to Germany to work at the Dr. Margarete Fischer Bosch Institute for Clinical Pharmacology, and the Robert Bosch Hospital in Stuttgart, where from 2007 till 2012, beside receiving his clinical training, he led an Emmy Noether Junior Research Group. A specialist in Clinical Pharmacology, he is currently also receiving training in Internal Medicine and Gastroenterology. In 2014 he was appointed to a professorial post at the University Hospital Tübingen. His main research interest lies in translating newly gained insights of relevance for the body's immune barrier into applied therapy.

COMPROMISED MUCOSAL ANTIMICROBIAL DEFENSE AS A DRIVER OF CHRONIC INTESTINAL INFLAMMATION

We survive because we adapted to a world of microorganisms. All our epithelial surfaces participate in keeping up an effective barrier against microbes while not initiating ongoing inflammatory processes and risking collateral damage to the host. Major players in this scenario are antimicrobial peptides (AMPs). AMPs participated in a preservative co-evolution with a complex microbiome. Particularly interesting interactions between host barrier and microbiota can be found in the gut. Crohn's disease of the small intestinal mucosa is associated with different defects of Paneth cells, an intestinal epithelial cell producing large amounts of antimicrobial peptides. Other mechanisms for distinct antimicrobial-defensin deficiencies are associated with the colonic type of Crohn's disease or ulcerative colitis. Recent research suggests that advancing our understanding of the circumstances of such interactions between gut microbiota and host AMPs should have therapeutic implications for different intestinal disorders.

STEPHAN C. BISCHOFF

UNIVERSITY OF HOHENHEIM

Studies of Medicine in Mainz/Germany and Strasburg/France. 1989 Research Fellow at the Institute for Clinical Immunology, University of Bern/Switzerland. 1992 Clinical Assistant at the Department of Gastroenterology, Hepatology and Endocrinology, University Medical School of Hannover, Germany. 1998 Assistant Professor and Board Member of the Boards of Specialists in Gastroenterology, Allergology and Nutritional Medicine. 2002 Associate Professor of the Hannover Medical School. 2002-03 Visiting Professor at Columbia University, New York. 2004 Nominated Full Professor and Chair of Nutritional Medicine and Prevention at the University of Hohenheim in Stuttgart/Germany. 2006-2010 Vice Dean of the Faculty of Life Sciences, Since 2007 Executive Director of the Institute for Nutritional Medicine of the University of Hohenheim and Medical Co-Director of the Center of Nutritional Medicine of the Universities of Hohenheim and Tübingen. Incorporator of the German Society of Mucosal Immunology. 2012-14 President of the German Society for Nutritional Medicine.

JULIA-STEFANIE FRICK

UNIVERSITY HOSPITAL TÜBINGEN

Professor Julia Frick studied medicine in Ulm. After her studies, she went on to specialize in medical microbiology at the Institute of Medical Microbiology and Hygiene at the University Hospital of Tübingen. In 2012 she was appointed Professor for Mucosal Immunology and Microbiome at the Institute of Medical Microbiology and Hygiene at the University Hospital of Tübingen. Her research focus lays on the role of commensal bacteria-host interactions in the development or prevention of systemic or intestinal chronic inflammatory or infectious disorders. Her work centers on the identification of commensal bacteria or components of commensal bacteria preventing systemic or intestinal inflammation, characterization of the interaction between commensal bacteria and the intestinal host target cells that result in prevention of inflammation and the identification of the cell signalling processes induced by commensal bacteria and supporting maintenance of intestinal homeostasis.

DIRK HALLER

TECHNICAL UNIVERSITY OF MUNICH

Dirk Haller studied food technology and Nutrition Science at the University of Hohenheim (1990-1997) and received his Ph.D. in Microbiology and Immunology in 1999. He worked for a year at the Nestlé Research Center in Switzerland before continuing his research as a DFG Emmy Noether fellow at the University of North Carolina (2001-2002) and the Technical University of Munich (2003-2006) where he became Associate professor in 2006 and advanced to a full professorship in 2008. As Professor of Nutrition and Immunology and head of the department of Nutrition and Food Sciences his research activities are focused on the basic understanding of the role of nutrition and the gut microbiome in the initiation, prevention and therapy of chronic inflammatory diseases, specifically focusing on inflammatory bowel diseases and intestinal tumorigenesis. Prof. Haller and his group are among the leading publishing experts on the interactions between microbiota, nutrition and gut health targeting novel mechanisms in chronic intestinal inflammation. He is the main founder and coordinator of the DFG Priority Program “Intestinal microbiota – a microbial ecosystem at the edge of immune homeostasis and inflammation”.

PHILIP ROSENSTIEL

UNIVERSITY OF KIEL

Philip Rosenstiel studied medicine in Kiel and Boston and graduated in 2001. During his studies he was awarded a research scholarship from the BMEP. He spent this time at the laboratories of Patsy Nishina (Jackson Lab, Maine) and Jeffrey Isner (St. Elisabeth Medical Center, Tufts University) working on mouse genetics and gene therapy. He received his M.D. degree on the characterization of a neurotrophic factor in 2003. As a postdoc, he then moved to the Dept. of Medicine in Kiel for medical training in Mucosal Immunology with Ulrich Fölsch and Stefan Schreiber. During that time he worked as a delegated postdoc at the MPI of Molecular Genetics in Berlin. Currently, he holds a professorship in Molecular and Evolutionary Medicine at the University of Kiel. He also serves as a member on the steering committees of several large-scale consortia in human disease research (e.g. ICGC MMML-Seq, Excellence Cluster Inflammation at Interfaces, SysMEDIBD, EMED). In 2012 Philip Rosenstiel became Director of the Institute of Clinical Molecular Biology.

HARTMUT WEKERLE

MAX PLANCK INSTITUTE OF NEUROBIOLOGY

Hartmut Wekerle was director and member of the Max Planck Institute of Neurobiology. In 2012 he was awarded a Hertie Senior Professorship, and he leads an Extended Emeritus Group.

Hartmut Wekerle's scientific research focuses on the mechanisms initiating and driving multiple sclerosis and its experimental models, which imply autoimmune attacks against the nervous system. Wekerle's work led to the identification of brain reactive autoimmune T lymphocytes in the immune system. Most recently, he identified the commensal bacterial gut flora as a factor triggering the pathogenic potential of immune cells. He develops and uses new imaging approaches to detail the mechanisms of autoimmune T cell migration into the brain. Wekerle has received numerous awards, including the Jung Prize, Zülch Prize, Koetser Prize, Charcot Award (MS International Federation), Grand Prix Louis D. (Institut de France), and a Koselleck Award (DFG). He holds an Honorary Professorship of the University of Munich and Honorary Doctorates of the Universities of Hamburg and Würzburg. He is a member of the German Academy of Science (Leopoldina).

NOTES

INFORMATION

CONFERENCE VENUE

Herrenhausen Palace
Herrenhäuser Straße 5
30419 Hanover
Germany

CONTACT

Anna Böhning (Project Manager, Event Department)
0049 (0)511 / 83 81-279
boehing@volkswagenstiftung.de
Dr. Oliver Grewe
(Program Director, Funding Department)
grewe@volkswagenstiftung.de

CONFERENCE WEBSITE

www.volkswagenstiftung.de/microbiome