Nationale Forschungsplattform für Zoonosen

International

Workshop

Intestinal mucosal homeostasis and disease

March 23 – 24, 2011 – Hannover

Conference Volume

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WELCOME NOTES

Welcome

It is our great pleasure to invite you to attend the international workshop “Intestinal mucosal homeostasis and disease” on March 23-24, 2011 in Hannover, Germany. The meeting is organized by the National Research Platform for Zoonoses in cooperation with the ZooMAP research consortia and the International Graduate School for Infection Research of the Helmholtz-Zentrum für Infektionsforschung.

Despite intense research, the etiological factors contributing to the pathogenesis of chronic inflammatory intestinal diseases in both humans and animals are still unknown. There is increasing evidence that in addition to genetic factors, alterations of the homeostasis between the host’s enteric mucosal surface and the intestinal microflora play a critical role.

The workshop aims to gather established internationally recognized specialists of various research disciplines related to intestinal homeostasis and disease in order to reinforce and intensify an interdisciplinary discussion. Scientific topics include various aspects of the intestinal mucosal barrier under physiological conditions and inflammation-driven alterations of the mucosal homeostasis in humans and animals.

The invited and internationally highly recognized speakers are selected experts in the various aspects of intestinal homeostasis and disease. Their presentations will provide an overview on the current knowledge but also highlight the most recent research and discoveries.

We greatly look forward to welcoming you in Hannover.

Ralph Goethe Mathias Hornef Siegfried Weiß

GENERAL INFORMATION

Scientific committee and organization
Mathias Hornef | Hannover
Ralph Goethe | Hannover
Siegfried Weiß | Braunschweig
Tina Basler | Hannover
Gerlinde Benninger | Münster
Sabine Kirchhoff | Braunschweig

Offical language
The official language of the meeting is English. Simultaneous translation will not be provided.

Meals
Lunches will be provided at the venue as indicated in the programme. Evening meal will be provided as part of the social programme. You are invited by the organizers.

Social programme
The conference dinner will take place at the Restaurant im Rathaus. The restaurant is located at Trammplatz 2, D-30159 Hannover. We propose to meet at 20.00 hrs.
Address: Restaurant im Rathaus, Trammplatz 2, D-30159 Hannover

Contact
National Research Platform for Zoonoses
c/o Institute of Molecular Virology (IMV)
Center of Molecular Biology of Inflammation (ZMBE)
Westfälische Wilhelms-Universität Münster
Von-Esmarch-Str. 56
D-48149 Münster
Phone: +49 (0)2 51/83 53011
Fax: +49 (0)2 51/83 57793
EMail: isabell.schmid@ukmuenster.de

PROGRAMME

Final programme

February 3, 2011

Nationale Forschungsplattform für Zoonosen

Welcome

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We greatly look forward to welcoming you in Hannover.

Ralph Goethe | Mathias Hornef | Siegfried Weiß

Wednesday, March 23, 2011

08.00 Registration

08.45 Opening
Ralph Goethe, Hannover
Mathias Hornef, Hannover
Siegfried Weiss, Braunschweig

09.00 – 11.00 Innate recognition & inflammation
Nod proteins in inflammation and disease
| Dana Philpott, Toronto
Macrophages in intestinal homeostasis and inflammation **| Allan Mowat, Glasgow**
TLR5 SNPs – naughty or nice?
| Dirk Werling, London (London)

11.00 Coffee break

11.30 – 13.00 Soluble factors & neuronal signals
A novel actor in charge of mucosal homeostasis: the digestive neuro-glial epithelial unit
| Michel Neunlist, Nantes
IL10- and IL10 receptor mutations in patients with early-onset inflammatory bowel disease
| Erik Glocker, London

13.00 Lunch

14.00 – 16.00 Barrier formation & microbiota
The mucus protecting system of the gastrointestinal tract **| Gunnar Hansson, Gothenburg**
Antimicrobial peptides and the regulation of the intestinal microbiota **| Nita Salzmann, Wisconsin**
Immune cell-microbial interactions in the gut
| David Artis, Philadelphia

16.00 Coffee break

16.30 – 18.30 Commensals & pathogens
Interactions between the adaptive immune system and intestinal microbiota in neonatal pigs: controlling mucosal tolerance at the effector stage
| Michael Bailey, Bristol
Listeria monocytogenes, a silent invader.
| Marc Lecuit, Paris
Salmonella diarrhea: subverting host defenses to gain a competitive edge
| Wolf-Dietrich Hardt, Zürich

20.00 Conference Dinner at the Restaurant im Rathaus

Thursday, March 24, 2011

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Endoplasmic reticulum stress at the epithelial surface **| Arthur Kaser, Cambridge**
Regulation of intestinal mucosal injury and repair by toll like receptors in the developing intestine
| David Hackam, Pittsburgh
The intestinal epithelium - active player in the host microbial interaction **| Mathias Hornef, Hannover**

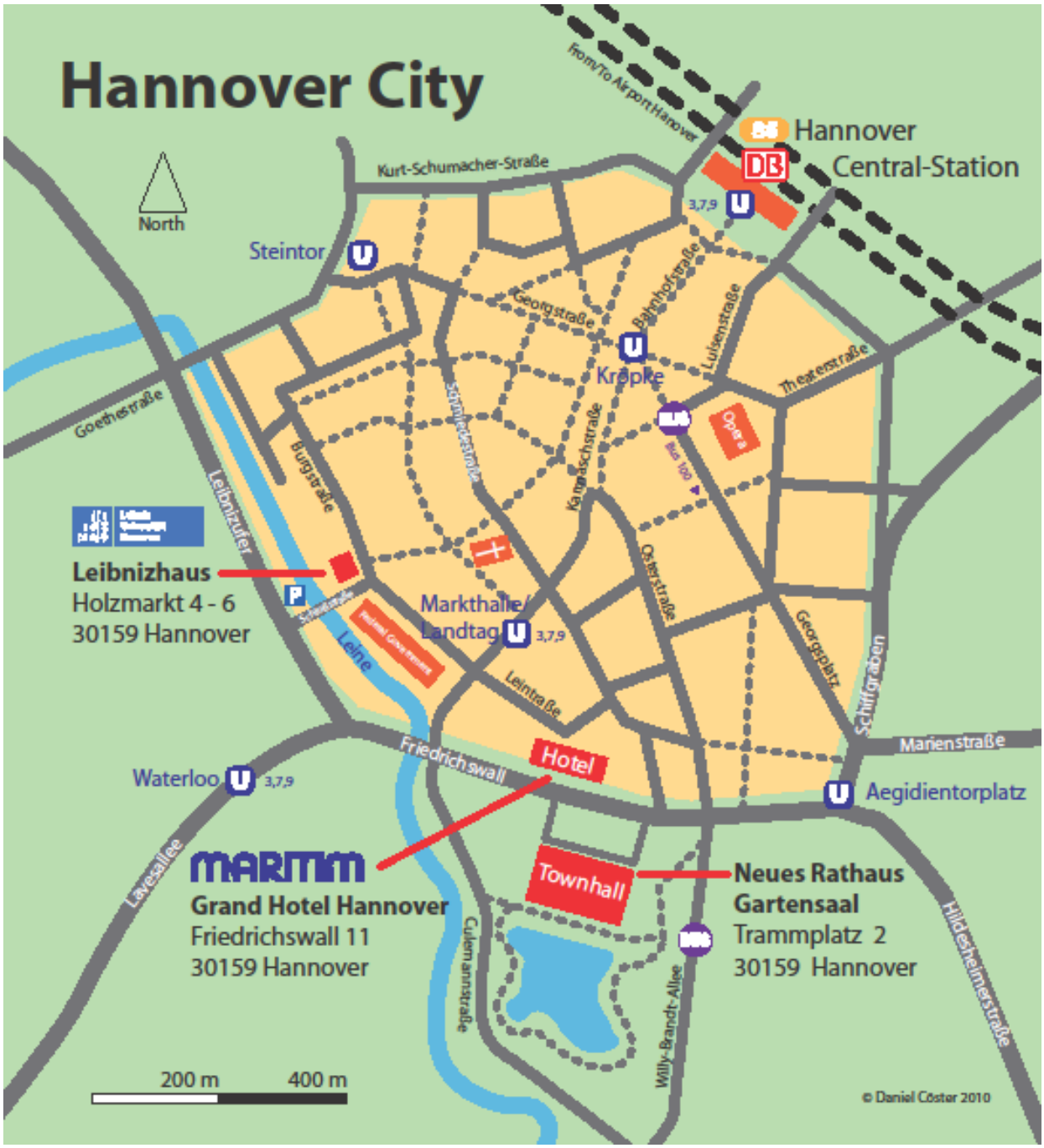
10.30 Coffee break

11.00 – 12.30 Mucosal homeostasis
Intestinal Microbiota and post natal maturation of the immune system **| Nadine Cerf-Bensussan, Paris**
Gut, germs and genes **| Eyal Raz, San Diego**
Genetic analysis of homeostatic controls in the intestinal epithelium of Drosophila
| Bruce Edgar, Heidelberg

12.30 Closing remarks

13.00 Lunch

VENUE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ORAL PRESENTATIONS

Innate recognition & inflammation

Wednesday, March 23, 2011

Chair: Christine Josenhans, Hannover, Germany

Nod proteins control early inflammatory responses at the intestinal mucosa important for pathogen clearance

Dana Philpott, Toronto, Canada

Macrophages in intestinal homeostasis and inflammation

Allan Mowat, Glasgow, UK

TLR5 SNPs – naughty or nice?

Dirk Werling, London, UK

Nod proteins control early inflammatory responses at the intestinal mucosa important for pathogen clearance

Kaoru Geddes[1], Stephen J. Rubino[2], Joao G. Magalhaes[1], Catherine Streutker[3], Lionel Le Bourhis[1], Kyle Cho[1], Stephen E. Girardin[2] , and Dana J. Philpott[1].

[1]Depts. of Immunology, [2]Laboratory Medicine and Pathobiology, and [3]Department of Laboratory Medicine, St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada M5S 1A8

Nod1 and Nod2 are innate immune receptors that detect peptidoglycan (PG) from the bacterial cell wall and trigger inflammation. Although both of these members of the Nod-like receptor (NLR) family respond to PG they respond to distinct substructures of this complex microbial-associated molecular pattern (MAMP). Indeed, Nod1 recognizes diaminopimelic acid-containing tripeptide fragments of PG, found mainly in Gram-negative bacteria, while Nod2 detects muramyl dipeptide, which is the minimal fragment of PG common to both Gram-negative and Gram-positive organisms. Detection of these muropeptides by Nod1 and Nod2 triggers a signal transduction cascade that culminates in the activation of NFkB and the production of pro-inflammatory mediators. Importantly, Nod1 and Nod2 have been implicated in inflammatory bowel disease (IBD), in particular Nod2 has been associated with Crohn's disease, yet a clear understanding of how dysfunctional Nod activation leads to aberrant inflammation is still lacking. While much of our previous work has focused on dissection of Nod signalling in in vitro and ex vivo models, our current interest is to understand how Nods function at the mucosal surface of the gastrointestinal tract and how they orchestrate inflammation and combat enteric infection. Specifically, we are interested in using bacterial colitis models, including the *Citrobacter rodentium* and *Salmonella typhimurium* models to probe Nod responses at the level of the intestinal mucosa. Our overall goal is to understand how Nod activation orchestrates mucosal responses and to delineate the functional importance of Nod triggering in order to gain a more complete understanding of their role in IBD.

Key words: Nod proteins, inflammation, intestinal mucosa, bacterial infection

Macrophages in intestinal homeostasis and inflammation

Allan McI Mowat, Calum C. Bain, Yvonne Bordon, Andrew M. Platt

Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK

A number of potent regulatory mechanisms ensure that inflammatory conditions such as coeliac disease and inflammatory bowel diseases are not generated in the intestine against harmless antigens in foods and commensal bacteria. These mechanisms include tolerogenic dendritic cells (DC) that ensure the generation of gut homing regulatory T cells and a large, resident population of macrophages (mΦ) that are unresponsive to inflammatory stimuli. Until recently, it has been difficult to discriminate clearly between these cells phenotypically and many cell populations have been ascribed wrongly to the different groups. Using refined multi-parameter flow cytometric analysis of mouse colon we show that DC and mΦ can be distinguished on the mutually exclusive expression of CD103 and CX3CR1. In the resting gut, virtually all mΦ are CD11bhi F4/80hi class II MHC+ CX3CR1hi Ly6Clo and are unresponsive to TLR stimulation. However they show constitutive production of both IL10 and TNFα, indicating that they are responding continuously to their environment in a balanced manner that ensures active tissue remodelling without overt inflammation. This probably accounts for the evidence that mΦ play an essential role in intestinal homeostasis. During experimental inflammation induced by feeding DSS, the colonic mΦ population changes dramatically, with the appearance of many CX3CR1int Ly6Chi cells which replace the resident mΦ. These are derived from CCR2-dependent recruitment of recently divided monocytes from the bone marrow and they respond vigorously to stimulation via TLR by production of pro-inflammatory cytokines. Preventing the recruitment of these inflammatory mΦ abolishes pathology in DSS colitis, suggesting that this strategy could provide the basis of therapy for inflammatory bowel disease in man. However a small number of CX3CR1int Ly6Chi mΦ is present in normal colon, raising the question of how these cells are related to the majority population of CX3CR1hi mΦ and how their potentially inflammatory properties are controlled under resting conditions. By defining these relationships, we aim to understand if targeting inflammatory mΦ could be a safe and selective means of treating disease without interfering with physiological processes.

TLR5 SNPs – naughty or nice?

D. Werling

Royal Veterinary College, Department of Pathology and Infectious Diseases, Hawkshead Lane, Hatfield, AL97TA, UK

The innate immune system provides the first line of host defense against invading pathogens. Innate immune responses are initiated by germline-encoded pattern-recognition receptors (PRR), which recognize specific structures expressed by microorganisms. Toll-like receptors (TLR) are a family of PRR which sense a wide range of microorganisms, including bacteria, fungi, protozoa and viruses. Due to their large surfaces in direct contact with the environment, mucosal tissues are the major sites of PAMP-TLR signalling, and are critical for intestinal homeostasis. These microbial sensors recognize components of the bacterial cell wall and its appendages. For example, TLR4 detects lipopolysaccharide in the Gram-negative bacterial cell wall. TLR5 recognizes flagellin, a component of bacterial flagella required for motility. How innate and adaptive immunity are triggered through flagellin-TLR5 interaction is the main focus of our on-going work. Here, I will describe the role of genetic polymorphism in TLR5 of cattle and dogs, the potential changes in susceptibility to mucosal infections and will present data showing a clear correlation of TLR5 SNPs with the development of IBD in dogs.

Key words: TLR5, flagellin, ruminant, canine

Soluble factors & neuronal signals

Wednesday, March 23, 2011

Chair: Oliver Pabst, Hannover, Germany

A novel actor in charge of gut mucosal homeostasis: the neuro-glio epithelial unit

Michel Neunlist, Nantes, France

Monogenic causes for early-onset inflammatory bowel disease

Erik-Oliver Glocker, London, UK

A novel actor in charge of gut mucosal homeostasis: the neuro-glio epithelial unit

M Neunlist, L Van Landeghem, M Mahe, E Coron, M Flamant, K Ngohou-Bach, G Meurette, A Bourreille, M Rolli-Derkinderen.

UMR Inserm U913; Institut of Digestive Diseases; University of Nantes, France

Intestinal epithelial barrier (IEB) functions play a key role in gut health and diseases. IEB functions are regulated by the cellular components of its microenvironment such as immune cells, fibroblasts or the microbiota. Over the past years, the digestive or enteric nervous system (ENS) has been identified as another major regulator of IEB functions. These studies have set the basis for the existence of a neuro-glio epithelial unit in the gut reminiscent to the neuro-glio endothelial unit controlling blood brain barrier functions in the brain. The ENS (also named the 2nd brain) is composed of neurons and glial cells organized into two major plexus all along the gastrointestinal tract. This presentation will be organized in three parts. A first part will summarize the latest advances demonstrating the protective effects of neurons and enteric glial cells upon barrier functions (permeability, proliferation) and discuss key neuro-glio mediators involved in these effects. A second part of the talk aims at supporting the concept that pathologies with IEB dysfunctions such as IBD or IBS can be associated or even due to enteric neuropathies. In a final part, the rational for developing therapeutical approaches using neurostimulation or nutritional targeting of the ENS to enhance its barrier protective effects will be discussed.

Key words: enteric neurons, enteric glial cells, intestinal epithelial barrier functions, inflammation

Monogenic causes for early-onset inflammatory bowel disease

Erik-Oliver Glocker

Department of Immunology & Molecular Pathology, University College London Medical School (Royal Free Campus), London, United Kingdom

Inflammatory bowel disease (IBD) is caused by dysregulation of the immune system and is characterised by a chronic and relapsing course with abdominal pain, diarrhoea, bleeding and malabsorption. It comprises the major forms Crohn's disease (CD) and ulcerative colitis (UC) as well as indeterminate colitis with overlapping features of CD and UC. The disease affects about 2.2 millions in Europe and 1.4 million people in the USA. The incidence of IBD in the United Kingdom amounts to 5-10/100,000 individuals with Crohn's disease and 10-20/100,000 for ulcerative colitis.

IBD usually manifests in the second or third decade of life, but it may also present in infancy with a severe and therapy resistant course of the disease.

Comprehensive research work on the pathogenesis suggests that IBD results from disturbed interactions between the innate and adaptive immune system and commensal bacteria of the gut. Genetic studies identified a variety of genes that may render individuals more susceptible to IBD, thereby indicating the complexity and multifactorial genesis of IBD.

We recently demonstrated that early-onset IBD may be monogenic: homozygous point mutations in the IL10 receptor genes *IL10RA* and *IL10RB* cause severe difficult-to-treat colitis in small children. This discovery enabled us to carry out a successful curative haematopoietic stem cell transplantation (HSCT) in one of the affected patients. A similar phenotype is observed in infants with homozygous point mutations in IL10, who present with a massive therapy-refractory colitis and severe perianal disease.

These findings not only highlight the vital role of IL10 in keeping the immune system in balance, they also suggest that in a subgroup of patients IBD is distinct from classical forms such as CD or UC.

Key words: IBD, auto-immunity, IL10, IL10 receptor

Barrier formation & microbiota

Wednesday, March 23, 2011

Chair: Gerald-F. Gerlach, Hannover, Germany

The mucus protecting system of the gastrointestinal tract

Gunnar Hansson, Gothenburg, Sweden

Antimicrobial peptides and the regulation of the intestinal microbiota

Nita Salzman, Wisconsin, USA

Regulation of innate and adaptive immunity at barrier surfaces

David Artis, Philadelphia, USA

The mucus protecting system of the gastrointestinal tract

Gunnar C. Hansson

Dept. Medical Biochemistry, University of Gothenburg, Gothenburg, SWEDEN

The large surface of the gastrointestinal tract is covered with a single layer of active cells and that have to have additional protection systems. This is made up by the mucus that covers and protects these cells. However, the system differs along the tract in that it has a single layer of non-attached mucus in the small intestine, whereas the stomach and large intestine have a two layered system. Especially the large intestine is difficult to protect as it harbors an enormous amount of bacteria. This was difficult to understood until we recently could show that the inner of the two mucus layers of colon are impermeable to bacteria. These mucus layers are built around the large MUC2 mucin, a protein that is assembled into enormous net-like polymers that can form a gel. These net-like polymers are secreted by the goblet cells together with a number of other components that we have discovered by proteomics. Several of these are likely to be important for building a stable inner mucus layer that is attached to the epithelia. The inner mucus layer is renewed in 1-2 hours and converted to an outer layer that is expanded in volume four times. This outer layer is the habitat for the commensal bacterial flora. If the MUC2 mucin is absent, there is no inner mucus and the bacteria come in direct contact with the epithelia, penetrate into the crypts and into the cells. This causes inflammation, bloody diarrhea and later on colon cancer, identical to what is observed in the disease ulcerative colitis. The concept and implications of the mucus layers for the protection of especially the large will be discussed.

Antimicrobial peptides and the regulation of the intestinal microbiota

N. H. Salzman[1,3,4], E. Worthey[3], D. Eastwood[5], G.M. Weinstock[8], C.L. Bevins[6], C.B. Williams[2,3], C. Kristich[4], and N.A. Bos[7].

[1]Division of Gastroenterology, [2]Division of Rheumatology, Department of Pediatrics, [3]Children's Research Institute, Department of [4]Microbiology and Molecular Genetics, and [5]Division of Biostatistics, Medical College of Wisconsin, Milwaukee, WI
[6]Department of Microbiology and Immunology, University of California Davis School of Medicine, Davis, CA
[7]Department of Cell Biology, Immunology Section, University Medical Center Groningen, University of Groningen, the Netherlands
[8]The Genome Center, Department of Genetics, Washington University in St. Louis School of Medicine, St. Louis, MO

Antimicrobial peptides are important effectors of innate immunity throughout the plant and animal kingdoms. In the mammalian intestine, there are several sources of antimicrobial peptides, including neutrophils, epithelial cells, and bacteria. Paneth cells, located at the bases of the small intestinal crypts are the primary epithelial source of antimicrobial peptides in the small intestine. Paneth cells produce abundant quantities of α-defensins, antimicrobial peptides that contribute to host defense against enteric pathogens. To determine if α–defensins also govern intestinal microbial ecology, we analyzed the intestinal microbiota in mice expressing the human Paneth cell α-defensin, HD5, and in mice lacking an enzyme required for processing of murine α-defensins. We detected significant α-defensin-dependent changes in microbiota composition, but not in total bacterial numbers, in these complementary models. Furthermore, HD5-expressing mice had striking losses of Segmented Filamentous Bacteria and fewer interleukin 17-producing lamina propria T cells. This suggests that defensins may regulate mucosal immune tone by their modulation of the composition of the intestinal microbiota. Antimicrobial peptides from non-epithelial sources also modulate the microbiota composition, further complicating the dynamic interactions that contribute to homeostasis at the intestinal mucosal surface.

Key words: Paneth cells, antimicrobial peptides, defensins, microbiota

Regulation of innate and adaptive immunity at barrier surfaces

David Artis

University of Pennsylvania, Philadelphia, USA

Intestinal epithelial cells (IECs) were recently shown to play a critical role in maintaining the balance of tolerance, immunity and inflammation in the gastrointestinal tract. Based on these findings, there are three major research areas in the lab. First, we are employing inducible deletion or overexpression of genes in IECs to interrogate how they regulate the functions of intestinal myeloid and lymphocyte lineages. The long-term goals of these studies are to improve oral vaccination against enteric infections and prevent chronic inflammation associated with diseases including food allergy and inflammatory bowel disease. Second, we are employing gnotobiotic mice to examine the influence of commensal microbial communities on intestinal and peripheral immune cell development and function. Our findings indicate that commensal microbes have a major regulatory influence on CD4+ T cell and granulocyte function associated with susceptibility to multiple inflammatory diseases. To determine if the immune system reciprocally regulates the acquisition and/or composition of commensal microbial communities, we are undertaking high-throughput pyrosequencing analyses of bacterial communities in murine models of health and disease. Third, we are investigating how IECs regulate allergen- or helminth-induced type 2 inflammation at mucosal sites. Secretion of IEC-derived cytokines including IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) appear to be important early events in influencing dendritic cell and CD4+ T cell responses required these responses. Our recent studies suggest that IECs also govern extramedullary hematopoiesis that can influence the development of T_H2 cytokine responses. It is hoped that the results of these studies will advance understanding the pathophysiology of multiple mucosal inflammatory diseases, including asthma, allergy and inflammatory bowel disease and provide a framework to test the therapeutic potential of manipulating IEC responses in these disease states.

Commensals and pathogens

Wednesday, March 23, 2011

Chair: Petra Dersch, Braunschweig, Germany

Interactions between the adaptive immune system and intestinal microbiota in neonatal pigs: controlling mucosal tolerance at the effector stage
Michael Bailey, Bristol, UK

Listeria monocytogenes **targets luminally accessible intestinal E-cadherin and is rapidly translocated into the lamina propria**
Marc Lecuit, Paris, France

Salmonella **diarrhea: subverting host defenses to gain a competitive edge**
Wolf-Dietrich Hardt, Zürich, Switzerland

Interactions between the adaptive immune system and intestinal microbiota in neonatal pigs: controlling mucosal tolerance at the effector stage

M. Bailey

School of Veterinary Science, University of Bristol, Langford House, Langford, Bristol, UK

There is increasing evidence that expansion of a competent immune system in neonates depends on the composition of the intestinal microbiota and therefore exposure to environmental microbes. However, the mechanisms linking early-life environment to later development of allergy in human infants are only just starting to be clarified. The extent of the changes in the lifestyles of humans (as a consequence of the development of agriculture and industrialization) are matched by those of our domesticated animals as a consequence of increasing intensification of agriculture. By rearing piglets under different conditions - either left to suckle the mother on the farm (low hygiene) or removed to an SPF isolator and fed milk formula (high hygiene) - we have demonstrated significant effects of rearing environment on the intestinal microbiota and on gene expression in the intestine. Specifically, the rearing environment of piglets affects the subsets of dendritic cells which are initially recruited to the intestinal lamina propria shortly after birth. By the time of weaning, rearing environment has affected numbers of effector and regulatory CD4+ T-cells in the intestinal mucosa, and these changes are correlated with the development of antibody responses to food antigens at weaning. We propose that these observations are causally linked: early colonization with microbiota affects dendritic cell recruitment (presumably by PRR signaling), and that this affects the later balance of regulatory and effector function in the mucosal immune system. As a corollary, it may be possible to influence mucosal immune function in humans and domesticated animals by microbial intervention during early life.

Key words: neonate, pig, immune response, environment

Listeria monocytogenes targets luminally accessible intestinal E-cadherin and is rapidly translocated into the lamina propria

Georgios Nikitas[1], Chantal Deschamps[1], Théodora Niault[1], Pascale Cossart[2], Marc Lecuit[1,3]

[1] Microbes & host barriers Group, Institut Pasteur, Inserm, Paris-F

[2] Bacteria-cell interactions Unit, Institut Pasteur, Inserm, Inra, Paris-F

[3] Paris-Descartes University, Department of Infectious Diseases, Necker-Enfants malades hospital, Paris-F

Listeria monocytogenes (*Lm*) is a foodborne pathogen that can cross the intestinal, blood-brain and placental barriers, leading to gastroenteritis, meningo-encephalitis and maternal-fetal infections. After ingestion, *Lm* adheres to intestinal epithelial cells via the binding of its surface protein InlA to its host receptor, E-cadherin (Ecad). Ecad mediates the formation of *adherens* junctions between epithelial cells and is located below tight junctions at the lateral cell-to-cell contacts of polarized epithelial cells.

InlA interaction with Ecad is species-specific, as it occurs in human but not in mice. In a humanized transgenic mouse model expressing human E-cadherin, *Lm* interacts with enterocyte hEcad, translocates across the epithelial intestinal barrier, multiplies in the lamina propria and disseminates to mesenteric lymph nodes, liver and spleen.

To decipher the cell biology of *Lm* trans-epithelial passage and its underlying molecular mechanisms, we have used the intestinal ligated loop system and two-photon microscopy, and studied the translocation of *Lm* across the intestinal epithelium *in vivo.*

We will present data that demonstrate that E-cadherin is luminally accessible on specific subtypes of epithelial cells constitutive of the intestinal barrier, and will present the molecular mechanisms underlying *Lm* rapid transfer in the lamina propria.

Salmonella diarrhea: subverting host defenses to gain a competitive edge

Wolf-Dietrich Hardt

Institute of Microbiology, ETH Zürich, Switzerland

Salmonella typhimurium is a well-known cause of diarrhea. For a long time, the virulence factors eliciting disease have been studied in vitro and host cell manipulation by this pathogen is quite well understood. However, these in vitro studies could not answer how this pathogen triggers disease in the host's intestine and how it might benefit from this. To address these central questions of *Salmonella* biology, we have developed the "streptomycin mouse model". This has allowed identifying virulence factors of the pathogen and elements of the host's defense which contribute to disease. I will discuss recent data on the importance of triggering gut inflammation for invading the intestinal ecosystem and a novel in vivo microscopy approach for analyzing pathogen invasion into the gut tissue. The latter approach identified a novel epithelium sampling pathway of the gut associated immune system. This sampling pathway is engaged by *S. typhimurium* for colonizing the cecal lamina propria.

Epithelial cell

Thursday, March 24, 2011

Chair: Peter Valentin-Weigand, Hannover, Germany

Endoplasmic reticulum stress at the epithelial surface
Arthur Kaser, Cambridge, UK

Regulation of intestinal mucosal injury and repair by toll like receptors in the developing intestine
David Hackam, Pittsburgh, USA

The intestinal epithelium - active player in the host microbial interaction
Mathias Hornef, Hannover, Germany

Endoplasmic reticulum stress at the epithelial surface

A. Kaser

Div of Gastroenterology and Hepatology, Dept of Medicine, University of Cambridge, Addenbrooke's Hospital, Level 5, Box 157, Cambridge, CB2 0QQ, United Kingdom

Endoplasmic reticulum (ER) stress arises due to the accumulation of unfolded or misfolded proteins in the ER, which initiates the Unfolded Protein Response (UPR), an adaptive response that temporarily halts protein translation and transactivates a specific transcriptional programme aimed. The intestinal epithelium may be considered a highly secretory organ, in particular due to the substantial protein production burden of specialized epithelial cells, Paneth cells and goblet cells. Hypomorphic function of the evolutionary most conserved effector arm of the UPR, X-box binding protein-1 (XBP1) specifically in the intestinal epithelium results in the spontaneous development of small intestinal inflammation with histologic hallmarks of human inflammatory bowel disease (IBD). Moreover, the *XBP1* locus and hypomorphic rare variants of this gene have been associated with genetic risk for both forms of IBD, Crohn's disease und ulcerative colitis. In addition, genome-wide association studies (GWAS) have discovered additional genetic IBD risk loci that functionally map to the ER stress response. A hallmark of hypomorphic XBP1 function is the profound hyperreactivity of the intestinal epithelium toward microbial molecules (like TLR ligands) and toward inflammatory mediators secreted from mucosal, including myeloid, cells. Deletion of *Xbp1* in the intestinal epithelium also leads to depletion of Paneth cells and a consequent functional impairment in the capacity of intestinal epithelial cells to handle orally infected bacterial model organisms, which allows important predictions on an altered handling of the commensal microbiota in the presence of a hypomorphic UPR. The UPR hence plays a major role in affecting the intestinal bacterial constituents, while at the same time determining the inflammatory reactivity of the epithelium toward these constituents.

Key words: inflammatory bowel disease, unfolded protein response, microbiota

Regulation of intestinal mucosal injury and repair by toll like receptors in the developing intestine

David J. Hackam, MD, PhD

Watson Family Professor of Surgery
Professor of Surgery, Cell Biology and Physiology
University of Pittsburgh School of Medicine
Attending Pediatric Surgeon
Children's Hospital of Pittsburgh of UPMC

Necrotizing enterocolitis (NEC) is a disease of premature infants that is characterized by intestinal inflammation and impaired mucosal healing, and occurs after the infant small intestine is colonized by microbes. The Hackam laboratory has demonstrated that the development of NEC requires activation of the gram negative bacterial receptor toll like receptor 4 (TLR4), as mice with mutations in TLR4 are protected from the development of this disease. To define the cellular and molecular pathways by which TLR4 activation leads to NEC in the premature intestine, the Hackam lab generated an intestinal-specific TLR4 knockout mouse (villin-TLR4$^{-/-}$), which was protected from the development of NEC as compared with wild-type counterparts, confirming that TLR4 signaling on the prenatal intestinal epithelium is required for NEC development. In seeking to understand the mechanisms by which TLR4 activation on the intestinal epithelium leads to NEC, Hackam and colleagues have shown that TLR4 activation in the newborn ileum leads to a marked increase in enterocyte death via apoptosis, and a marked reduction in mucosal healing through direct inhibition of intestinal stem cell proliferation. These findings have led to an in silico based strategy for the identification of novel anti-TLR4 compounds, that have preliminarily shown clinical efficacy in mouse models, through the optimization of intestinal repair and limitation of TLR4-induced intestinal injury.

The intestinal epithelium – active player in the host microbial interaction

Johanna Pott, Tamas Dolowschiak, Claudia Dürr, Silvia Stockinger, Cécilia Chassin, Aline Dupont, Evalotte Decker and Mathias Hornef

Institute for Medical Microbiology and Hospital Epidemiology, Hannover Medical School, Hannover, Germany

Innate immune receptors recognize evolutionary conserved essential microbial constituents that are found both in pathogenic as well as environmental and commensal microorganisms. Receptor activation results in the initiation of signal transduction cascades and the transcriptional activation of proinflammatory mediators such as chemokines. Strikingly, innate immune receptor expression is not restricted to professional immune cells but also found on epithelial cells at many body surfaces. Although mechanisms must exist that prevent an inappropriate epithelial activation by commensal bacteria and environmental microbial stimuli, intestinal epithelial cells might contribute to recognize and combat microbial challenge at an early stage during infection. Our work therefore focusses on mechanisms that prevent an inappropriate epithelial stimulation by commensal bacteria and the role of epithelial innate immune receptor expression and host defence activation to combat infection with enteropathogenic microorganisms. Here we present recent results that demonstrate communication between neighbouring intestinal epithelial cells facilitating a coordinated epithelial response to microbial challenge. This mechanism significantly enhances the chemokine secretion in response to infectious challenge and restricts immune evasion strategies of pathogenic microorganisms. In addition we demonstrate the efficacy of epithelial-specific host defence activation and its functional role during microbial challenge *in vivo*.

Mucosal homeostasis

Thursday, March 24, 2011

Chair: Sebastian Suerbaum, Hannover, Germany

Influence of intestinal microbiota on host immune system

Nadine Cerf-Bensussan, Paris, France

Gut, germs and genes: the role of the microflora in intestinal oncogenesis

Eyal Raz, San Diego, USA

Intestinal stem cell control by signaling interactions in the healthy and hyperplastic *Drosophila* gut

Bruce Edgar, Heidelberg, Germany

Influence of intestinal microbiota on host immune system

Nadine Cerf-Bensussan

INSERM U989, Université Paris Descartes

The intestine is an open ecological system that is colonized immediately after birth by a microbial population, which reaches an impressive density of 10^{12} bacteria per gram of luminal content in the distal gut. The notion is emerging that hosts and their gut microbiota form superorganisms in which energy and metabolites are exchanged while homeostasis is maintained by the immune system.

In the mammalian gut, innate and adaptive immune mechanisms have evolved into a complex system (Gut-associated-lymphoid tissue: GALT). GALT development is initiated before birth by a genetic program. Its full maturation however occurs only after birth and is strictly dependent on microbiota-derived signals. Recent studies have highlighted how the microbiota elicits innate and adaptive immune mechanisms that cooperate to protect the host, maintain intestinal homeostasis and build an efficient barrier against invasive pathogens. An important challenge is currently to understand whether and how individual members of the microbiota or microbiota-derived products may affect the balance between pro-inflammatory and regulatory immune responses, and to establish whether the composition of the microbiota can influence the development of inflammatory diseases within and beyond the gut. We will show how gnotobiotic mice represent a powerful tool to address these issues.

Gut, germs and genes: the role of the microflora in intestinal oncogenesis

Eyal Raz, M.D

Department of Medicine 0663, University of California San Diego, La Jolla California, USA

TLR signaling is essential for intestinal tumorigenesis in *Apc*$^{min/+}$ mice, but the mechanisms by which this protein enhances tumor growth are unknown. Here we show that the Microflora-MyD88-ERK signaling in intestinal epithelial cells (IEC) promotes tumorigenesis by increasing the stability of the c-myc oncoprotein. Activation of ERK phosphorylates c-myc that prevents its ubiquitination and its subsequent proteasomal degradation. Accordingly, *Apc*$^{min/+}$*/Myd88*$^{-/-}$ mice display reduced levels of pERK and c-myc proteins in IEC, and a low incidence of IEC tumors. A MyD88-independent activation of ERK by EGF increases pERK and c-myc levels and restores the Min phenotype in *Apc*$^{min/+}$*/Myd88*$^{-/-}$ mice. Administration of an ERK inhibitor suppressed intestinal tumorigenesis in EGF-treated *Apc*$^{min/+}$*/Myd88*$^{-/-}$ and in *Apc*$^{min/+}$ mice and increased their survival. Our data reveal a new facet of oncogene-environment interaction, where the microflora-induced TLR activation regulates the expression of an oncogene that leads to IEC tumor growth in a susceptible host**.**

Intestinal stem cell control by signaling interactions in the healthy and hyperplastic *Drosophila* gut

Huaqi Jiang[1], Parthive H. Patel[2], Alexander Kohlmaier[2], Rachael Shaw[3], Nic Tapon[3], and Bruce A. Edgar[2, 1]

[1]Division of Basic Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, Seattle, WA 98109, USA,
[2]DKFZ-ZMBH Alliance, Im Neuenheimer Feld 282, D-69120 Heidelberg, Germany,
[3]Cancer Research UK, London Research Institute, 44 Lincoln's Inn Fields, London, WC2A 3PX, United Kingdom

Cells in intestinal epithelia turn over rapidly due to aging, damage, and toxins produced by the enteric microbiota. Gut homeostasis is maintained by intestinal stem cells (ISCs) that divide to replenish the intestinal epithelium, but relatively little is known about how ISC division and differentiation are coordinated with gut epithelial cell loss. Loss of stem cell control in the intestine leads to important human diseases, such as polyposis syndromes (FAP, JPS), inflammatory bowel diseases, and colorectal cancer. We have been using the *Drosophila* intestine (midgut) as a model system for genetic analyses of intestinal homeostasis. We find that when intestinal enterocytes (ECs) in the fly midgut are subjected to apoptosis, enteric infection, or JNK-mediated stress signaling, the intestinal epithelium and visceral muscle respond by producing cytokines (Upd, Upd2, Upd3) and growth factors (Vn, Krn, Spi). These ligands activate Jak/Stat and EGFR/Ras/MAPK signaling in intestinal stem- and progenitor-cells, and thereby promote ISC division and gut renewal. This function extends to healthy midguts, which maintain low levels of cytokine and growth factor expression, Stat activity, and MAPK activity in stem cells, and require EGFR/Ras signaling for ISC proliferation and Jak/Stat signaling for differentiation. Thus cytokine- and EGFR/Ras/MAPK-mediated feedback between differentiated enterocytes and intestinal stem cells plays a central role in both stress-induced gut regeneration and normal gut homeostasis. In addition to studying normal ISCs, we are investigating the biology of stem cell tumors generated by either the loss of Notch/Delta signaling, or the loss of Hippo signaling. *Notch* mutations generate stem cell tumors by blocking ISC differentiation, whereas *Hippo* pathway mutations drive hyperplasia while allowing differentiation. In both cases, however, tumor growth involves and requires the non-cell autonomous stimulation of cytokine and growth factor production by the transformed tumor cells. Given the extensive similarities of the cellular and molecular biology of the fly and human intestines, such signaling interactions are likely to play roles in human intestinal homeostasis and disease.

PARTICIPANTS

A

Akineden, Ömer
Justus-Liebig-Universität Gießen
Gießen, Germany
Oemer.Akineden@vetmed.uni-giessen.de

Artis, David
University of Pennsylvania
Philadelphia, USA
dartis@vet.upenn.edu

B

Bailey, Michael
University of Bristol
Bristol, UK
mick.bailey@bristol.ac.uk

Bargen, Imke
Helmholtz-Zentrum für Infektionsforschung
Braunschweig, Germany
imke.bargen@helmholtz-hzi.de

Bartonickova, Lucie
Medizinische Hochschule Hannover
Hannover, Germany
bartonickova.lucie@mh-hannover.de

Basic, Marijana
HZI Graduate School
Braunschweig, Germany
marijana.basic@gmail.com

Basler, Tina
Tierärztliche Hochschule Hannover
Hannover, Germany
tina.basler@tiho-hannover.de

Baumann, Ulrich
Medizinische Hochschule Hannover
Hannover, Germany
Baumann.u@mh-hannover.de

Behrens, Wiebke
Medizinische Hochschule Hannover
Hannover, Germany
behrens.wiebke@mh-hannover.de

Belismelis, Ana
Tierärztliche Hochschule Hannover
Hannover, Germany
abelismelis@yahoo.de

Bleich, Andre
Medizinische Hochschule Hannover
Hannover, Germany
bleich.andre@mh-hannover.de

Bönig, Tobias
Medizinische Hochschule Hannover
Hannover, Germany
boenig.tobias@mh-hannover.de

Bruder, Dunja
Helmholtz-Zentrum für Infektionsforschung
Braunschweig, Germany
dunja.bruder@helmholtz-hzi.de

Busse, Friedrich-Wilhelm
SES, Zentrale Bonn
Bonn, Germany
lirebusse@aol.com

C

Cerf-Bensussan, Nadine
Université Paris Descartes-Faculté de Médecine
Paris, France
nadine.cerf-bensussan@inserm.fr

Chassin, Cecelia
Medizinische Hochschule Hannover
Hannover, Germany
cecilia.chassin@gmail.com

Chopra, Himpriya
Medizinische Hochschule Hannover
Hannover, Germany
chopra.himpriya@gmail.com

Coombs, Nina
Medizinische Hochschule Hannover
Hannover, Germany
coombs.nina@mh-hannover.de

D

Dersch, Petra
Helmholtz-Zentrum für Infektionsforschung
Braunschweig, Germany
pde08@helmholtz-hzi.de

Dolowschiak, Tamas
Medizinische Hochschule Hannover
Hannover, Germany
dolowschiak.tamas@gmail.com

Duerr, Claudia
Medizinische Hochschule Hannover
Hannover, Germany
duerr.claudia@gmail.com

Dupont, Aline
Medizinsche Hochschule Hannover
Hannover, Germany
dupont.aline@mh-hannover.de

E

Ebner, Florian
University of Vienna
Vienna, Austria
florian.ebner@univie.ac.at

Eckelt, Elke
Tierärztliche Hochschule Hannover
Hannover, Germany
elke.eckelt@tiho-hannover.de

Edgar, Bruce
Deutsches Krebsforschungszentrum
Heidelberg, Germany
b.edgar@zmbh.uni-heidelberg.de

Eibach, Daniel
Medizinische Hochschule Hannover
Hannover, Germany
Eibach.Daniel@mh-hannover.de

Enss, Marie-Luise
Medizinsche Hochschule Hannover
Hannover, Germany
enss.marie-luise@mh-hannover.de

F

Fernandez-Silva, Jorge A.
Justus-Liebig-Universität Gießen
Gießen, Germany
jorge.a.fernandez-silva@vetmed.uni-giessen.de

Fischer, Marta
Justus-Liebig-Universität Gießen
Gießen, Germany
marta.fischer@vetmed.uni-giessen.de

G

Gehrken, Henning
Deutsche Veterinärmedizinische Gesellschaft
Gießen, Germany
Henning.Gehrken@gmx.de

Gereke, Marcus
Helmholtz-Zentrum für Infektionsforschung
Braunschweig, Germany
marcus.gereke@helmholtz-hzi.de

Gerhard, Ralf
Medizinische Hochschule Hannover
Hannover, Germany
gerhard.ralf@mh-hannover.de

Gerlach, Gerald F.
IVD GmbH
Hannover, Germany
gfgerlach@gmx.de

Gerstel, Ulrich
Universitätsklinikum Schleswig-Holstein
Kiel, Germany
Ugerstel@dermatology.uni-kiel.de

Giriprakash, Chodisetti
Medizinische Hochschule Hannover
Hannover, Germany
chgiriprakash@gmail.com

Glocker, Erik-Oliver
University College London
London, UK
eglocker@medsch.ucl.ac.uk

Goethe, Ralph
Tierärztliche Hochschule Hannover
Hannover, Germany
ralph.goethe@tiho-hannover.de

Goffe, Adeelia
Robert Koch-Institut
Berlin, Germany
goffea@rki.de

Guschlbauer, Maria
Tierärztliche Hochschule Hannover
Hannover, Germany
maria.guschlbauer@tiho-hannover.de

H

Hackam, David
Children's Hospital of Pittsburgh
Pittsburgh, USA
hackamd@upmc.edu

Hadis, Usriansyah
Medizinische Hochschule Hannover
Hannover, Germany
usriansyah@mh-hannover.de

Hainzl, Eva
University of Veterinary Medicine Vienna
Vienna, Austria
eva.hainzl@vetmeduni.ac.at

Hammerschmidt, Swantje
Medizinische Hochschule Hannover
Hannover, Germany
hammerschmidt.swantje@mh-hannover.de

Hansen, Gesine
Medizinische Hochschule Hannover
Hannover, Germany
Hansen.Gesine@mh-hannover.de

Hansson, Gunnar C.
University of Gothenburg
Gothenburg, Sweden
gunnar.hansson@medkem.gu.se

Hardt, Wolf-Dietrich
Eidgenössische Technische Hochschule Zürich
Zurich, Switzerland
hardt@micro.biol.ethz.ch

Heitkamp, Anne-Sophie
Medizinische Hochschule Hannover
Hannover, Germany
anne-sophie_heitkamp@web.de

Herbrand, Heike
Medizinische Hochschule Hannover
Hannover, Germany
herbrand.heike@mh-hannover.de

Hofreuter, Dirk
Medizinische Hochschule Hannover
Hannover, Germany
hofreuter.dirk@mh-hannover.de

Hornef, Mathias
Medizinische Hochschule Hannover
Hannover, Germany
hornef.mathias@mh-hannover.de

Huang, Yi-Ju
Helmholtz-Zentrum für Infektionsforschung
Braunschweig, Germany
Yi-Ju.Huang@helmholtz-hzi.de

J

Jacobsen, Ilse D.
Hans-Knöll-Institut
Jena, Germany
ilse.jacobsen@hki-jena.de

Janus, Lydia
Medizinische Hochschule Hannover
Hannover, Germany
janus.lydia@mh-hannover.de

Jerjomiceva, Natalja
Tierärztliche Hochschule Hannover
Hannover, Germany
natalja.jer@inbox.lv

Josenhans, Christine
Medizinische Hochschule Hannover
Hannover, Germany
josenhans.christine@mh-hannover.de

Jyotsana, Nidhi
Medizinische Hochschule Hannover
Hannover, Germany
jyotsana.nidhi@gmail.com

K

Kahlert, Stefan
Otto-von-Guericke-Universität Magdeburg
Magdeburg, Germany
stefan.kahlert@med.ovgu.de

Kaiser, Patrick
Eidgenössische Technische Hochschule Zürich
Zurich, Switzerland
kaiser@micro.biol.ethz.ch

Kaser, Arthur
University of Cambridge
Cambridge, UK
ak729@cam.ac.uk

Kennemann, Lynn
Medizinische Hochschule Hannover
Hannover, Germany
kennemann.lynn@mh-hannover.de

Kerner, Katharina
Friedrich-Loeffler-Institut
Jena, Germany
katharina.kerner@fli.bund.de

Klotz, Christian
Robert Koch-Institut
Berlin, Germany
klotzc@rki.de

Kluess, Jeannette
Otto-von-Guericke-Universität Magdeburg
Magdeburg, Germany
jeannette.kluess@med.ovgu.de

Koc, Arzu
Universitätsklinikum Gießen
Gießen, Germany
kocarzu@hotmail.de

Köhler, Heike
Friedrich-Loeffler-Institut
Greifswald-Insel Riems, Germany
heike.koehler@fli.bund.de

Kuemmel, Klaus
Klinikum Kulmbach
Kulmbach, Germany
klauskuemmel@hotmail.com

L

Luthje, Petra
Karolinska Institute
Solna, Sweden
Petra.Luthje@ki.se

Laarmann, Kristin
Tierärztliche Hochschule Hannover
Hannover, Germany
kristin.laarmann@gmx.de

Lecuit, Marc
National Reference Center & WHO-CC Listeria
Paris, France
marc.lecuit@pasteur.fr

Lim, Chee Han
Medizinische Hochschule Hannover
Hannover, Germany
lim.cheehan@mh-hannover.de

Lindner, Cornelia
Medizinische Hochschule Hannover
Hannover, Germany
conny.lindner@gmail.com

Lochner, Matthias
Twincore GmbH
Hannover, Germany
matthias.lochner@twincore.de

M

Merkel, Jörg
Tierärztliche Hochschule Hannover
Hannover, Germany
joerg.merkel@tiho-hannover.de

Möbius, Petra
Friedrich-Loeffler-Institut
Jena, Germany
petra.moebius@fli.bund.de

Meens, Jochen
Tierärztliche Hochschule Hannover
Hannover, Germany
jochen.meens@tiho-hannover.de

Meißner, Thorsten
Tierärztliche Hochschule Hannover
Hannover, Germany
meisek@web.de

Menge, Christian
Friedrich-Loeffler-Institut
Jena, Germany
christian.menge@fli.bund.de

Michael, Svenja
HZI Graduate School
Braunschweig, Germany
svenja.michael@onlinehome.de

Mowat, Allan
University of Glasgow
Glasgow, UK
a.m.mowat@clinmed.gla.ac.uk

N

Nell, Sandra
Medizinische Hochschule Hannover
Hannover, Germany
nell.sandra@mh-hannover.de

Nerlich, Andreas
Tierärztliche Hochschule Hannover
Hannover, Germany
andreas.nerlich@tiho-hannover.de

Neunlist, Michel
Institut des Maladies de l'Appareil Digestif
University Hospital
Nantes, France
Michel.Neunlist@univ-nantes.fr

Nomier, Yousra
Tierärztliche Hochschule Hannover
Hannover, Germany
yousra.nomier@tiho-hannover.de

P

Pabst, Oliver
Medizinische Hochschule Hannover
Hannover, Germany
Pabst.Oliver@MH-Hannover.de

Philpott, Dana
University of Toronto, Canada
Toronto, Canada
dana.philpott@utoronto.ca

Platz, Sabine
fzmb GmbH
Erfurt, Germany
splatz@fzmb.de

Pohl, Stefanie Claudia
Twincore GmbH
Hannover, Germany
stefanie.pohl@twincore.de

Pott, Johanna
Medizinische Hochschule Hannover
Hannover, Germany
pott.johanna@mh-hannover.de

R

Rauch, Isabella
Max F. Perutz Laboratories
Vienna, Austria
isabella.rauch@univie.ac.at

Raz, Eyal
University of California
San Diego, USA
eraz@ucsd.edu

Rogge, Kathleen
Helmholtz-Zentrum für
Infektionsforschung
Braunschweig, Germany
Kathleen.Rogge@helmholtz-hzi.de

Rosenheinrich, Maik
Universität Rostock
Rostock, Germany
maik.rosenheinrich@uni-rostock.de

Rothkoetter, Hermann-Josef
Otto-von-Guericke-Universität Magdeburg
Magdeburg, Germany
hermann-josef.rothkoetter@med.ovgu.de

Rummel, Andreas
Medizinische Hochschule Hannover
Hannover, Germany
rummel.andreas@mh-hannover.de

S

Sack, Meike
Tierärztliche Hochschule Hannover
Hannover, Germany
meike.sack@gmail.com

Salzman, Nita H.
Medical College of Wisconsin
Milwaukee, USA
nsalzman@mcw.edu

Sayed-Ahmed, Mohamed
Tierärztliche Hochschule Hannover
Hannover, Germany
drzakaria101@yahoo.com

Schulz, Olga
Medizinische Hochschule Hannover
Hannover, Germany
schulz.olga2@mh-hannover.de

Schwan, Carsten
Albert-Ludwigs-Universität Freiburg
Freiburg, Germany
carsten.schwan@pharmakol.uni-freiburg.de

Schweinlin, Matthias
Fraunhofer-Institut für Grenzflächen- und Bioverfahrenstechnik IGB
Stuttgart, Germany
Matthias.Schweinlin@igb.fraunhofer.de

Seele, Jana
Tierärztliche Hochschule Hannover
Hannover, Germany
jana_seele@gmx.de

Seidler, Ursula
Medizinische Hochschule Hannover
Hannover, Germany
seidler.ursula@mh-hannover.de

Seitz, Maren
Tierärztliche Hochschule Hannover
Hannover, Germany
maseitz@tiho-hannover.de

Stockinger, Silvia
Medizinische Hochschule Hannover
Hannover, Germany
stockinger.silvia@mh-hannover.de

Strotmeier, Jasmin
Medizinische Hochschule Hannover
Hannover, Germany
strotmeier.jasmin@mh-hannover.de

Suerbaum, Sebastian
Medizinische Hochschule Hannover
Hannover, Germany
suerbaum.sebastian@mh-hannover.de

Suwandi, Abdulhadi
Helmholtz-Zentrum für Infektionsforschung
Braunschweig, Germany
asu10@helmholtz-hzi.de

T

Tümmler, Burkhard
Medizinische Hochschule Hannover
Hannover, Germany
tuemmler.burkhard@mh-hannover.de

Taras, David
Lohmann Animal Health GmbH & Co. KG
Cuxhaven, Germany
colin.taras@lohmann.de

Tordy, Dominique
Fraunhofer-Institut für Grenzflächen- und Bioverfahrenstechnik IGB
Stuttgart, Germany
dominique.tordy@igb.fraunhofer.de

Torow, Natalia
Medizinische Hochschule Hannover
Hannover, Germany
Torow.Natalia@mh-hannover

U

Ugur, Milas
Medizinische Hochschule Hannover
Hannover, Germany
ugurmilas@gmail.com

V

Valentin-Weigand, Peter
Tierärztliche Hochschule Hannover
Hannover, Germany
peter.valentin@tiho-hannover.de

van Barneveld, Andrea
Medizinische Hochschule Hannover
Hannover, Germany
barneveld.andrea.van@mh-hannover.de

Volkmann, Maria
Freie Universität Berlin
Berlin, Germany
maria.volkmann@fu-berlin.de

von Köckritz-Blickwede, Maren
Tierärztliche Hochschule Hannover
Hannover, Germany
mkoeckbl@tiho-hannover.de

Willms, Daniela
Tierärztliche Hochschule Hannover
Hannover, Germany
daniela.willms@tiho-hannover.de

Wilsky, Steffi
Friedrich-Loeffler-Institut
Jena, Germany
steffi.wilsky@fli.bund.de

W

Wahl, Benjamin
Medizinische Hochschule Hannover
Hannover, Germany
wahl.benjamin@mh-hannover.de

Walk, Nicole
Otto-von-Guericke-Universität Magdeburg
Magdeburg, Germany
nicole.walk@med.ovgu.de

Wang, Zuobai
Twincore GmbH
Hannover, Germany
zuobai.wang@twincore.de

Weigoldt, Mathias
Tierärztliche Hochschule Hannover
Hannover, Germany
weigoldt@gmx.de

Weiß, Siegfried
Helmholtz-Zentrum für
Infektionsforschung
Braunschweig, Germany
siegfried.weiss@helmholtz-hzi.de

Werling, Dirk
The Royal Veterinary College
London, UK
dwerling@rvc.ac.uk

Werner, Carolin
Universität Hamburg
Hamburg, Germany
carolinwerner@yahoo.de

Willenborg, Jörg
Tierärztliche Hochschule Hannover
Hannover, Germany
joerg.willenborg@tiho-hannover.de

X-Z

Zautner, Andreas
Universitätsmedizin Göttingen
Göttingen, Germany
azautne@gwdg.de

Zimmermann, Kurt
Symbio Gruppe GmbH & Co. KG
Herborn, Germany
kurt.zimmermann@symbio.de

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