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Z.I.E.L.

ZENTRUM FÜR INFEKTION UND ENTZÜNDUNG LÜBECK

CENTER FOR INFECTIOUS DISEASES AND INFLAMMATORY MEDICINE LÜBECK

Scientific Report 2013–2015

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Scientific Report 2013–2015

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Scientific Report 2013–2015

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I About Z.I.E.L

I.1 Speaker's Statement

Rüdiger Labahn: *Professor Solbach, the establishment of the Center for Infection and Inflammation Research comes after a long process of development. The new building will provide a permanent base for research centered on the research focus of "Infection and Inflammation". You have witnessed the growth of this research focus, not only as a scientist, but also as Dean. Looking back, how do you reflect on the development process?*

Werner Solbach: Well, I am more than happy to reflect on what has been achieved in terms of the development of the new research Center, culminating in the ground breaking ceremony on the 2nd of July. The Z.I.E.L building is both a symbol and recognition of the successful work of the Z.I.E.L Historically, infection and inflammation are the oldest research foci of our University. Indeed, the first DFG funded Collaborative Research Center and the first Research Training Group here in Lübeck were established in this field in close collaboration with the Leibniz Research Center Borstel. The University has always been and still is very supportive in the development of infection and inflammation research. The research profile generated by these initiatives initially served as the basis for many successful regional, national and international consortia and made the University a highly recognized partner in formation of the Schleswig-Holstein Cluster of Excellence "Inflammation at Interfaces" and, more recently, during the establishment of the German Centers for Infection (DZIF) and Lung Research (DZL). The long-term strategic research planning decisions taken by the University have paid dividends; a view which is unequivocally shared by the German Council of Science and Humanities (Wissenschaftsrat).

There may have been some ups and downs along the way. Can you share these with us?

At the outset it is worth recognizing the unstinting support of University for Z.I.E.L researchers, not to mention the important financial backing. This support is a crucial motivation for researchers, enabling them to develop new research foci, and, in turn, to contribute to the research strength of the University. Indeed,

the latter is obvious when considering the external research funding which has been secured, including the Collaborative Research Center 654 on "Plasticity and Sleep" and, more recently, three Research Training Groups that have been granted by DFG[1], plus the recent awards of a clinical DFG research group[2] and, together with the University of Tübingen, a DFG Research Group.[3] These achievements have clearly raised our visibility on the national and international level. The portfolio will be extended to rheumatology, since the University and the University Clinic have founded a new Clinic for Rheumatology in 2014. Also, in late 2015 the former Institute for Medical Microbiology and Hygiene has been merged with part of the Medical Clinics III to the Department of Infectious Diseases and Microbiology. The clinical part is devoted to specialized on-site care for patients with severe infections. It is hoped that by bringing laboratory diagnostics and patient care under one organizational roof will facilitate clinical studies of high quality.

A setback came in 2010 with the intention of the former regional government to close the medical faculty of the University of Lübeck. However, that plan only served to catalyze huge support for the University not only from academics, but from the business community and the population of Lübeck. By working together and supporting each other, the campaign impressively demonstrated the importance of solidarity, ultimately preventing closure of the medical faculty. I hope that solidarity, teamwork and cooperation are borne in mind when facing the major challenges of today. I also hope that Government has learned to appreciate the importance of science.

What is the most effective strategy for developing successful scientific enterprise?

There is no single effective strategy applicable to all situations given the cultural differences between research fields. However, establishing a clear, long-term, over-arching research focus, which serves as basis for all strategic planning decisions, is crucial. In Lübeck, the key research topics of "Medical Technology", "Brain, Behavior and Metabolism", and "Infection and Inflammation" demonstrate our success in developing our research profile. I don't think that a small university could support more research themes. However, to avoid encrustation, new ideas and initiatives should be constantly monitored and, if excellent, should be fertilized for flourishment. In any case, excellent quality rather than the quantity of research is the key. As important as strategic planning is the devotion of researchers which automatically will inspire young people to develop their own agenda.

There are some problems that affect many centers with medical faculties and University Hospitals. Constraints on financing patient care prevent many hospitals from fulfilling their statutory obligations, i.e. to support research and deliver high quality teaching. The sometimes competing duty to provide state-of-the-art patient care at the same time may result in taking a "back seat" in research Consequently, it may become increasingly difficult to inspire the next generation of clinicians to perform research, given the lack of opportunities and clinic-free time. Indeed, these problems are recognized by Z.I.E.L and the University has decided to competitively finance "clinician scientist" stipends for medical doctors to do research work.

Moving back to the research foci of Z.I.E.L Reflecting on over 30 years of experience in the fields of Infection and Inflammation Research, what has changed? Are there major medical advances on the immediate horizon?

Let me set out three developments. The discovery of monoclonal antibodies has revolutionized medical diagnostics and therapy. Patients with autoimmune diseases or cancer have treatment options which were unthinkable less than a decade ago. This discovery was complimented by the second development, rapid advances in genetics. Such advances are providing detailed novel insights into biological processes and facilitate the road to what some call "personalized

1 RTG 1727 Modulation von Autoimmunität, Lübeck 2011; RTG 1743 Gene, Umwelt und Entzündung (in cooperation with the University of Kiel); Kiel; Borstel; Lübeck 2012; int. RTG 1911 Immunregulation der Entzündung bei Allergien und Infektionen Lübeck; Borstel; Cincinnati 2013;

2 KFO 303: Pemphigoid Diseases – Molecular Pathways and their Therapeutic Potential 2015

3 Forschergruppe 2327 VIROCARB: Glycans Controlling Non-Enveloped Virus Infections 2016

medicine". In my opinion, the next decade will provide opportunities to gain insight into "metagenomics" of the human and bacterial genome. Such opportunities are on the horizon by fascinating advances in medical technology, for example in the field of robotics, imaging or the big data revolution. Z.I.E.L is prepared for these challenges, last but not least by moving to the new building "cheek-to-cheek" to the recently opened "Center for Brain, Behavior and Metabolism" CBBM in 2019. This stimulating neighborhood will foster innovative ideas along both, the CBBM and the Z.I.E.L, missions, c. f. the important topic of "Metabolic inflammation".

What are your hopes for the future? Where do you see the Z.I.E.L in 20 years? And what is needed to make it possible?

WS: There will be as many unanswered questions in twenty years as are today. We will advance our understanding of allergies and destructive autoimmune processes, hopefully generate new antibiotics to treat multi-resistant bacteria, develop our understanding of the effects of the environment on our genome and practice personalized medicine. The Z.I.E.L will be part of these developments and make its contributions. Future has already started, since preparations for the national Excellence Initiative are in full swing.

Prof. Solbach, many thanks for the interview.

Professor Werner Solbach was interviewed by Rüdiger Labahn, Press Office of the University of Lübeck.

1.2 Research & Strategy

Scientific excellence at the University of Lübeck focuses on three major research areas: "Infection & Inflammation", "Brain, Behavior and Metabolism" and "Biomedical Engineering". These fields represent the university's largest consortia and contribute to numerous projects. They are flanked by cross-sectional profile areas like "Medical Genetics", "Population Medicine" "Cultural Studies" and "Translational Oncology".

The University's focus on "Infection & Inflammation" has always been at the core of its scientific activities and it looks back on more than two decades of constant growth and strategic development.

In 2011, the formal establishment of Z.I.E.L, the Center for Infectious Diseases and Inflammatory Medicine Lübeck, has integrated all research groups of this field into one future concept. Its executive board coordinates all relevant research activities on campus including Z.I.E.L's integration of various partners, such as the Research Center Borstel (Leibniz Center for Medicine and Biosciences), the Fraunhofer Research Institution for Marine Biotechnology and a wide range of national and international collaborative partners. The cornerstone for a central Z.I.E.L research building in June 2015 will pave the way for a joint scientific base that will enable all Z.I.E.L scientists to share and exchange their ideas, methods and techniques under one roof. The building is door-to-door to the newly established Center for Brain, Behavior and Metabolism and will foster transdisciplinary research in a hitherto unprecedented dimension.

Z.I.E.L scientists participate in joint research structures with a broad spectrum of third party funding. As a result of an international reviewing process Lübeck has been selected as a member institution of the German Centers for Health Research for both, respiratory (DZL) and infectious diseases (DZIF), and has been granted a national Cluster of Excellence on "Inflammation at Interfaces".

In order to strengthen Z.I.E.L's further development, the University of Lübeck has given priority to research on infection and inflammation by recruitment of leading professorships in Rheumatology and Pathology and by creating another seven professorships with tenure track options that will enhance expertise especially in Immunology, Dermatology, Pediatrics and Microbiology.

Image: *Model of the new building that will host Z.I.E.L researchers from 2019 on (hammeskrause architekten).*

Funding highlights for Z.I.E.L's investigators since 2013 have been the following regional as well as trans-regional programs:

DFG Coordinated Research Programs (German Research Foundation)

Cluster of Excellence EXC 306 "Inflammation at Interfaces" (ongoing, awarded 2007)

Transregional Collaborative Research Center 654 "Plasticity and Sleep" (ongoing, awarded 2005)

Transregional Collaborative Research Center 22 "Allergic Immune Response of the Lungs" (2009–2014)

Clinical Research Unit 303 "Pemphigoid Diseases – Molecular Pathways and their Therapeutic Potential" (ongoing, awarded 2015)

Research Unit 2327 VIROCARB: Glycans Controlling Non-Enveloped Virus Infections (ongoing, awarded 2016)

Clinical Research Unit 170 "Early pathogenesis of Granulomatosis with polyangiitis" (2007–2015)

BMBF Networks (Federal State Department for Education and Research)

DZIF – German Center for Infection Research (ongoing, awarded 2011, extended 2015)

DZL – German Center for Lung Research (ongoing, awarded 2011, extended 2015)

Tuberculosis: TB or not TB (ongoing, awarded 2010)

GNN – German Neonatal Network (ongoing, awarded 2009)

EU Consortia

PathoGenoMics (2010–2015)

SILVER – Small-molecule Inhibitor Leads Versus Emerging and neglected RNA viruses (2010–2014)

TB-PANNET – Study and Clinical Management of TB Drug Resistance (2009–2013)

Scientific collaboration at the University of Lübeck is embedded into the university's BioMedTec concept, a cooperation of research institutions and industrial partners on and around the campus. BioMedTec partners of the university include the University Hospital (UKSH), Lübeck's University of Applied Science, Leibniz Research Center Borstel and Fraunhofer Institute for Marine Biotechnology. In addition, a growing number of industrial partners extends BioMedTec's campus profile towards collaboration for knowledge transfer and biomedical engineering.

Trans-regional collaboration of Z.I.E.L's scientists is based on their broad participation in funding programs for joint research and receives international acknowledgement through individual partnerships that involve partners from European, US-American, Asian and, more recently, also to African institutions.

Examples for international relations in context of research on infections and inflammatory phenomena are:

– Multi-Sited PhD program of Lübeck's DFG- funded Research Training Group on "Immunoregulation of Inflammation in Allergy and Infection" in cooperation with Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, USA (PI: Prof. Dr. Jörg Köhl, Systemic Inflammation Research).

– DFG project for African collaboration on "Development of recombinant ELISA for diagnosis of Lassa fever in Africa and structural and biochemical characterization of the replication complex of Lassa virus" (Prof. Dr. Dr. h. c. R. Hilgenfeld, Biochemistry) and "Innate Immunity in Leishmaniasis" (Prof. Dr. T. Laskay, Medical Microbiology and Hygiene)

– State University for Medicine and Pharmacy, Chisinau, Moldova (USMF): DAAD Pagel project REACH-4-MOLDOVA (PIs: Prof. Dr. Dr. h. c. C. Lange, Research Center Borstel & Prof. Dr. J. Westermann, Anatomy)

– University of Namibia School of Medicine, Windhoek, Namibia: DAAD Pagel project afriCAN (PIs: Prof. Dr. Dr. h. c. C. Lange, Research Center Borstel & Prof. Dr. J. Westermann, Anatomy)

1.3 Education and Curricular Program

Z.I.E.L member institutions not only contribute to one of the focus areas of the curriculum at Lübeck Medical School, there has also been a research-based development of new educational programs in the field of infectious diseases and inflammatory medicine. The University of Lübeck offers a Bachelor and Master program for "Molecular Life Science" and a Master program for "Infection Biology". In addition, a central Graduate School for all PhD candidates has been established in 2014. The new Graduate School Lübeck (GSL) coordinates curricula, soft skill courses and administrative services for PhD programs, especially within Z.I.E.L's DFG funded Research Training Groups (RTGs):

DFG Coordinated Graduate Programs (German Research Foundation):

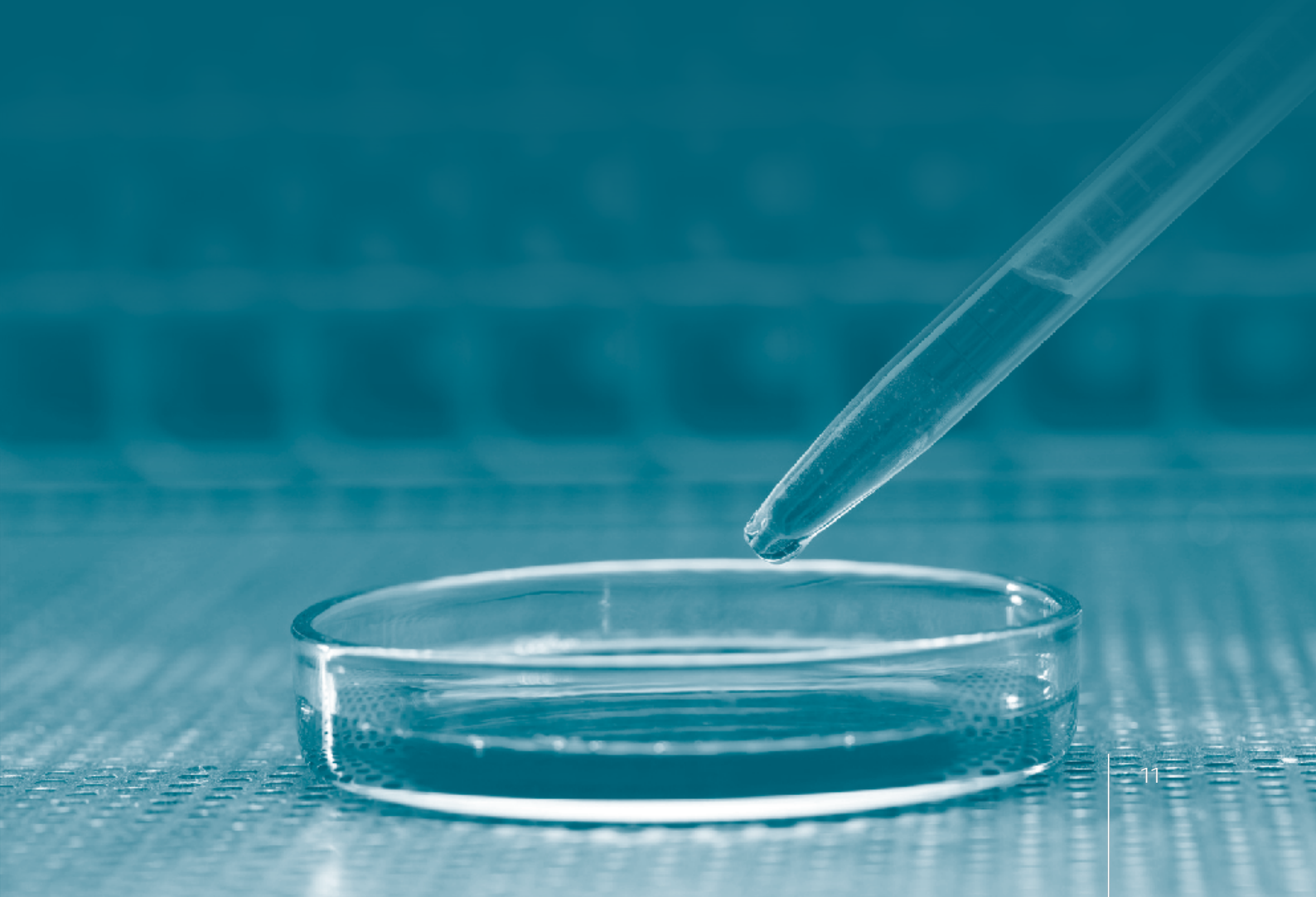
Research Training Group RTG 1727 "Modulation of Autoimmunity" (ongoing, awarded 2011, extended 2015)

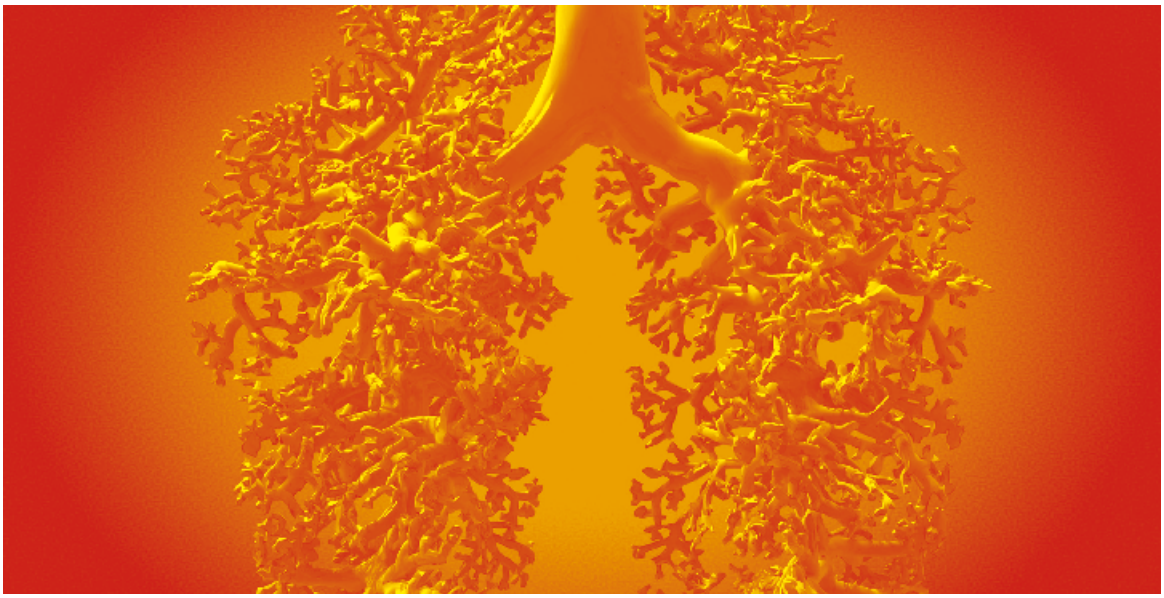
International Research Training Group iRTG 1911 "Immunoregulation of Inflammation in Allergy and Infection" (ongoing, awarded 2013); Partner: Research Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, USA (ongoing, awarded 2013)

Training Group RTG 1743 "Genes, Environment and Inflammation" (Speaker's Institution: University of Kiel, Germany) (ongoing, awarded 2012)

II Z.I.E.L Research Areas Characterization, Conflicts and Pathways

Z.I.E.L's research and development activities aim at exploring infectious diseases and inflammatory phenomena including the translation of its results into therapeutic strategies. Scientific projects currently focus on a set of infectious diseases as well as on mechanisms of innate and acquired immunity, including the illumination of underlying genetic factors. The following chapters exemplify some of the activities. Due to space restriction, not all of Z.I.E.L's more than 50 scientific groups are mentioned explicitly with apologies. However, a complete list of publications can be found in the Annex.





II.1 Infection & Inflammation: From Molecules to Clinical Application

II.1.1 Molecular Structures




N. Tautz, S. Taube, R. Hilgenfeld, T. Peters

The groups of Professor Taube (Institute for Virology and Cell Biology) and Professor Peters (Institute for Chemistry) have recently been awarded DFG grants within a DFG Research Group (FOR 1327). The aim of the consortium "VIROCARB" is the investigation of glycans controlling non-enveloped virus infections. Likewise in the group of Professor Tautz the regulation of genome replication and morphogenesis of particles is investigated for Flaviviruses. The group of Professor Hilgenfeld has contributed significantly to the characterization of Coronaviruses, a recent example being the MERS-Coronavirus. The results of this research can serve as ground-working knowledge for the development of small anti-infective molecules.

Publication highlights

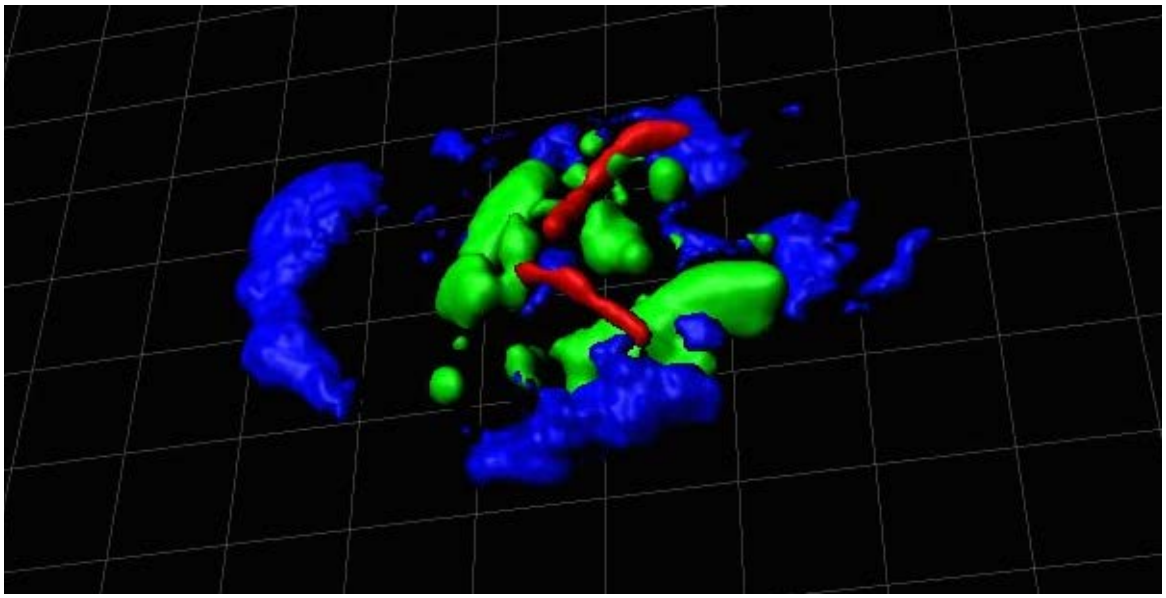
Mallagaray A, Lockhauserbäumer J, Hansman G, Uetrecht C, Peters T. **Attachment of norovirus to histo blood group antigens: a cooperative multistep process**. Angew Chem Int Ed Engl. 2015 Oct 5;54(41):12014-9. doi: 10.1002/anie.201505672. Epub 2015 Aug 19.

Taube S, Kolawole AO, Höhne M, Wilkinson JE, Handley SA, Perry JW, Thackray LB, Akkina R, Wobus CE. **A mouse model for human norovirus**. MBio. 2013 Jul 16;4(4). pii: e00450-13. doi: 10.1128/mBio.00450-13

Isken O, Langerwisch U, Jirasko V, Rehders D, Redecke L, Ramanathan H, Lindenbach BD, Bartenschlager R, Tautz N. **A conserved NS3 surface patch orchestrates NS2 protease stimulation, NS5A hyperphosphorylation and HCV genome replication**. PLoS Pathog. 2015 Mar 16;11(3):e1004736. doi: 10.1371/journal.ppat.1004736. eCollection 2015 Mar. Erratum in: PS Pathog. Erratum in: PS Pathog. 2016 Jan;12(1):e1005394

Hilgenfeld R. **From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design**. FEBS J. 2014 Sep;281(18):4085-96. doi: 10.1111/febs.12936. Epub 2014 Aug 11. Review.

Websites www.biochem.uni-luebeck.de | www.vuz.uni-luebeck.de | www.chemie.uni-luebeck.de



Infectious Diseases II.2

Z.I.E.L research groups investigate different entities within the exploration of mechanisms underlying the progression of infections.

Tuberculosis II.2.1

At Forschungszentrum Borstel (FZB), an institution within Germany's Leibniz-Gemeinschaft, the Priority Area Infections (PA Infections), coordinated by Professor Schaible and Professor Niemann, uses its multidisciplinary portfolio to study chronic infections of the lung with a strong focus on tuberculosis (TB). Tuberculosis (TB) has an enormous global impact on human health and ranges among the leading causes of deaths globally. The PA Infections has implemented TB research across its divisions to study this infectious disease from genomics to molecular structures, from cellular to animal models, from molecular surveillance and diagnosis and to patient care. This value-added chain of communicating basic and clinical research topics has the ultimate goal to improve prophylaxis, diagnosis, treatment and final outcome of TB.

With its TB research, the FZB has taken over a leading role in this field worldwide. It is one of the most important partners for clinical and basic research in infectious and inflammatory diseases of the University of Lübeck, and a preferred partner in national and international consortia such as the DZIF, Leibniz-Research Alliance Infections'21, TBNET, TB-PanNet, NAREB and Patho-NGen-Trace.

The division of Clinical Infectious Diseases, headed by Professor Lange, focuses on the development of personalized medicine in infections with both, *M. tuberculosis* as well non-tuberculosis mycobacteria (NTM) by identifying and evaluating novel biomarkers for point-of-care diagnosis and innovative therapeutic strategies with a focus on drug resistant TB patients (Horsburg et al., 2015). Professor Lange is coordinating national and multinational clinical research studies in the area of prevention, diagnosis and treatment of TB. The Division was chosen as the clinical reference center for TB in Germany and is instrumental in developing recommendations for the management of patients with mycobacterial infections (Zellweger et al. 2015; Günter et al., 2015; Sester et al., 2014).

Important clinical advances for treatment of TB have been achieved with regard to timing of diagnosis, and methods that will further optimize diagnostic accuracy. Clinical application of new drugs depends on

Image: *Imaging removal mycobacteria infected neutrophils by macrophages through efferocytosis: 3D reconstruction of an apoptotic human neutrophil (green) infected with the attenuated M. bovis BCG (red), which has been engulfed by a human macrophage (blue: NADPase oxidase).*

coordinated basic research. The interrelation of the two characterizes the successful strategy of FZB's contribution to combating TB.

Based on an evolutionary medicine concept, the division of Molecular and Experimental Mycobacteriology as headed by Professor Niemann co-leader of the National Reference Center for Mycobacteria at the FZB, applies a comprehensive translational research concept to study local / global dynamics of *M. tuberculosis* transmission esp. of drug resistant strains, resistance and compensatory mechanisms, global population structure and genomic diversity, mycobacterial virulence and pathobiology. The ultimate goal is to implement individualized therapy esp. for drugs resistant cases. The division introduced molecular genotyping techniques and next generation sequencing (NGS) genome analysis to study TB outbreaks (Roetzer et al. PLoS MED 2013, Merker et al. Nat Gen 2015). Prof Niemann coordinates the EU FP7-funded Patho-NGen-Trace project expected to produce new, next-generation sequencing (NGS) based tools for improved molecular surveillance and diagnostics of microbial pathogens. Currently, NGS is used to reveal transmission dynamics and evolution of multi-drug-resistant (MDR) *M. tuberculosis* strains in Eastern Europe and Africa, and to define the global impact of the spread of highly successful MDR strains (Comas et al. Nat Gen 2011, Merker et al. Nat Gen 2015, Sanchez-Padilla et al. NEJM 2015).

Professor Schaible's division of Cellular Microbiology studies host-pathogen interactions in TB on molecular, cellular and animal model levels. The division

C. Lange, U. Schaible, S. Niemann

asks how the intracellular niche of *M. tuberculosis* determines the pathogens fate and transmission, innate and acquired immunity and pathogenesis and, ultimately, drug efficacy. Analysis of mycobacterial factors and host target structures regarding intracellular intracellular survival revealed the mycobacterial glycolipid, trehalose dimycolate (TDM) as a factors which blocks phagosome maturation. The interactome between host cell and TDM revealed strong association with cytoskeleton (Kolonko et al., 2013) and interference with pro-inflammatory responses through IL-10 induction by Mincle signaling (Patin et al, 2016). Furthermore, lipid metabolisms related enzymes such as the lysosomal phospholipase A2 are relevant for protective immunity in TB (Schneider et al, 2014). Focusing on the role of neutrophils in TB, we found that these cells fail to eliminate *M. tuberculosis* but are driven into necrotic cell death by infection thereby contributing pathogenesis. Within national and international networks (CNV, DZIF, NAREB), we study novel nanoparticles for vaccine and drug development against TB (Leidinger et al., 2015). Finally, considering the lung microenvironment as determinant for local infection immunity, we pivotally identified a murine lung microbiota (Yun et al 2014).

Publication Highlights

Merker M, et al., Supply P, Niemann S (equal contribution), Wirth T. Evolutionary history and global spread of the Mycobacterium tuberculosis Beijing lineage. Nat Genet 2015 47(3):242-9.

Günther G, van Leth F, Alexandru S, Altet A, Avsar K, Bang D, Barbuta R, Bothamley G, Ciobanu A, Crudu V, Davilovits M, Dedicoat M, Duarte R, Gualano G, Kunst H, de Lange W, Leimane V, Magis-Escurra C, McLaughlin AM, Muylle I, Polcová V, Pontali E, Popa C, Rumetshofer R, Skrahina A, Solodovnikova V, Spinu V, Tiberi S, Viiklepp P, Lange C, for the TBNET. Multidrug-resistant tuberculosis in Europe: A TBNET study. Emerg Infect Dis 2015 Mar;21 (3):409-16.

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Sester M, van Leth F, Bruchfeld J, Bumbacea D, Cirillo DM, Dilektasli AG, Domínguez J, Duarte R, Ernst M, Eyuboglu FO, Gerogianni I, Girardi E, Goletti D, Janssens JP, Julander I, Lange B, Latorre I, Losi M, Markova R, Matteelli A, Milburn H, Ravn P, Scholman T, Soccal PM, Straub M, Wagner D, Wolf T, Yalcin A, Lange C for the TBNET. **Risk assessment of tuberculosis in immunocompromised patients. A TBNET study**. Am J Respir Crit Care Med 2014 Nov 15; 190(10):1168-76.

Sanchez-Padilla E, Merker M, et al., Niemann S. **Detection of drug-resistant tuberculosis by Xpert MTB / RIF in Swaziland**. N Engl J Med 2015 19; 372(12):1181-2.

Yun Y, Srinivas G, Kuenzel S, Linnenbrink M, Alnahas S, Bruce KD, Steinhoff U, Baines JF, Schaible UE. **Environmentally determined differences in the murine lung microbiota and their relation to alveolar architecture**. PLoS One. 2014 Dec 3;9(12):e113466.

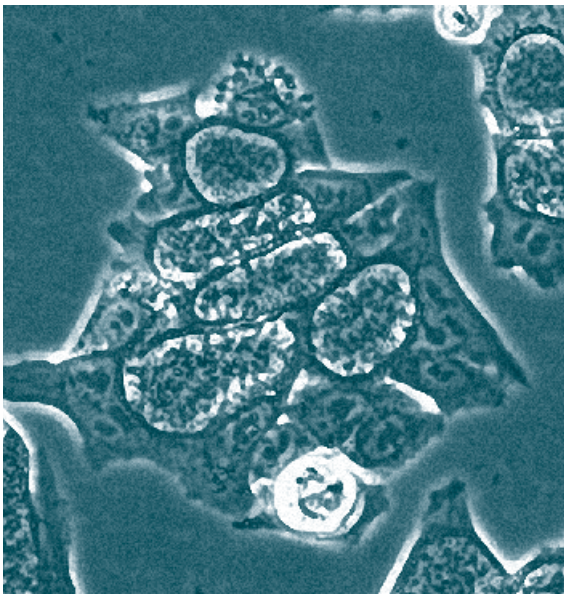
Roetzer A, Diel R, et al., Niemann S. **Whole genome sequencing versus traditional genotyping for investigation of a Mycobacterium tuberculosis outbreak: a longitudinal molecular epidemiological study**. PLoS Med. 2013 (2):e1001387.

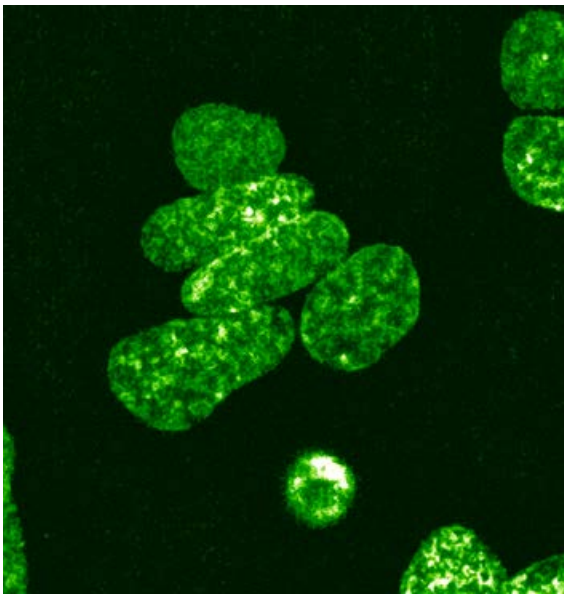
Reiling N, Homolka S, et al., Niemann S. **Clade-specific virulence patterns of Mycobacterium tuberculosis complex strains in human primary macrophages and aerogenically infected mice**. MBio 2013 Jul 30;4(4).

Selected Partners

German Center for Infection Research (DZIF); Karolinska Institute, Stockholm, Sweden; Karlsruhe Institute of Technology (KIT), Baden; State University for Medicine and Pharmacy, Chisinau, Republic of Moldova; University of Namibia School of Medicine, Windhoek, Namibia.

Website www.fz-borstel.de





II.2.2 Host-Pathogen Interactions

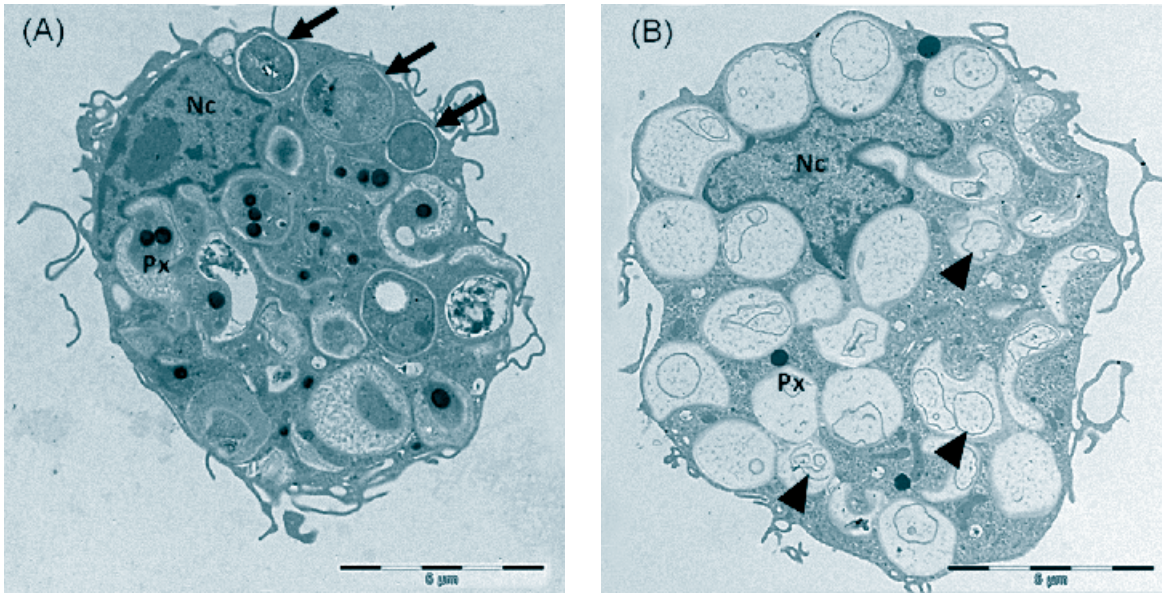
J. Rupp

Human pathogenic Chlamydiae infect the respiratory tract, the eyes and the urogenital tract. *C. pneumoniae* infects the upper and lower respiratory tract particular in children and young adults and has been attributed in its persistent form to the pathogenesis of COPD and asthma. Infections with *C. trachomatis* is the most frequent sexually transmitted disease worldwide, causing severe sequelae like salpingitis, pelvic inflammatory disease and infectious infertility in females. Pathogenetic features in Chlamydia infections are strongly connected to a particular intracellular developmental cycle that allows the pathogen to promote active growth but also to silently persist depending on nutrient availability or changing microenvironmental factors.

For better characterization of environmental factors that have a direct impact on chlamydial progeny and pathogenicity we developed *ex vivo* infection models of the airways and the upper female genital tract, making use of surgical specimens of the lung and the fallopian tubes. In addition we succeeded for the first time to genetically modify Chlamydiae that will allow a better characterization of pathogenic factors that support intracellular survival and host immune escape. Functional analysis of the intracellular metabolic activity is performed by 2-photon laser scanning microscopy and the Seahorse Bioanalyzer that allows to particularly determining mitochondrial and glycolytic activity of infected cells and tissues.

In addition to investigations on host-pathogen interactions we are focusing on a more life-like prediction of the anti-chlamydial efficacies of already known and novel antimicrobials. Considering environmental factors in experimental drug-testing, e.g. a low oxygen environment in the female urogenital tract, turned out to be an important factor determining intracellular efficacies of currently recommended drugs like azithromycin, doxycycline and rifampicin. Changes in the microbiota are currently investigated in different clinical cohorts (fertile / infertile females, female sex workers) to characterize the microenvironmental conditions favoring chlamydial infections which will be tested in a recently mice infection model. In collaboration with George Deepe / Cincinnati we apply the established models to infections with *Histoplasma capsulatum* extending our knowledge about general principles in the control of intracellular pathogens.

Image: *C. trachomatis in cell culture (green)*



Publication Highlights

Bollinger T, Bollinger A, Gies S, Feldhoff L, Solbach W, Rupp J. **Transcription regulates HIF-1α expression in CD4+ T cells**. Immunol Cell Biol 2016; 94(1):109-13.

Käding N, Szaszák M, Rupp J. **Imaging of Chlamydia and host cell metabolism**. Future Microbiol. 2014;9(4):509-21. Review.

Bollinger T, Gies S, Naujoks J, Feldhoff L, Bollinger A, Solbach W, Rupp J. **HIF-1α- and hypoxia-dependent immune responses in human CD4+CD25high T-cells and T-helper 17 cells**. J Leukoc Biol 2014; 96(2):305-12.

Szaszák M, Steven P, Shima K, Orzekowsky-Schröder R, Hüttmann G, König IR, Solbach W, Rupp J. **Fluorescence lifetime imaging unravels C. trachomatis metabolism and its crosstalk with the host cell**. PLoS Pathogens 2011;7: e1002108.

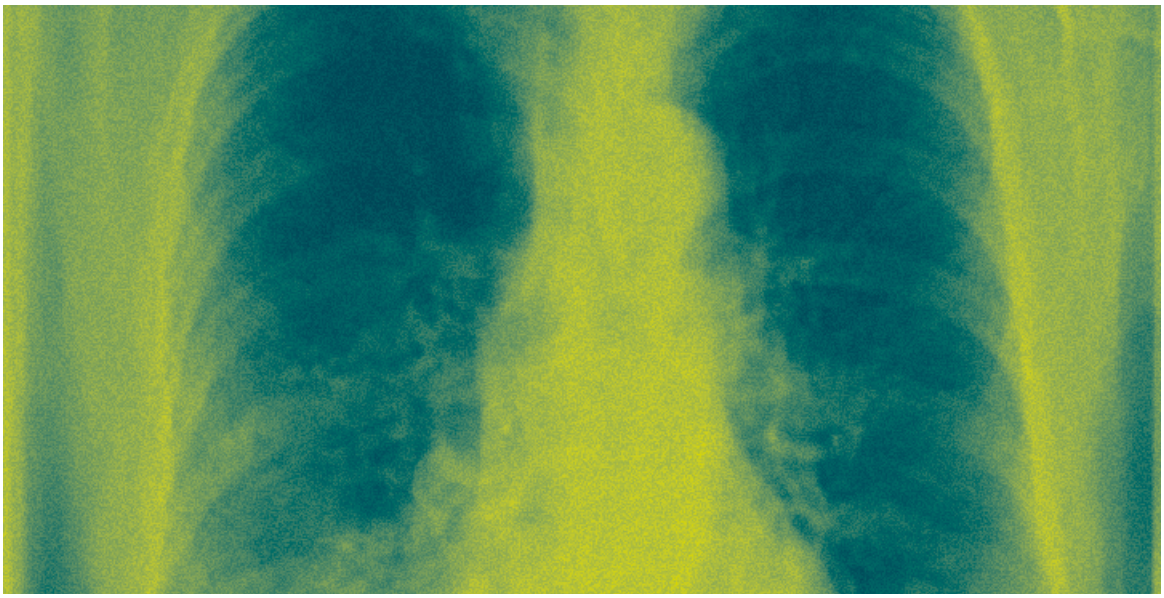
Roth A, König P, van Zandbergen G, Klinger M, Hellwig-Burgel T, Daubener W, Bohlmann MK, Rupp J. **Hypoxia abrogates antichlamydial properties of IFN-gamma in human fallopian tube cells in vitro and ex vivo**. Proc Natl Acad Sci U S A 2010; 107:19502-7.

Selected Partners

Helmholtz Zentrum München – German Research Center for Environmental Health, Munich; Department of Microbiology and Ecosystem Science, Vienna, Austria; University of Cincinnati College of Medicine, Cincinnati, USA; Cellular Biology of Microbial Infection / Institute Pasteur, Paris, France.

Website www.uksh.de/Infektiologie_Mikrobiologie

Image: *Transmission electron microscopy (TEM) images of MΦ infected with viable (A) and heat killed Histoplasma capsulet (Hc) (B). While Hc survives inside the host cell (A, black arrows), heat killed Hc are degraded (B, arrowhead) within 24h p.i.*



II.2.3 COPD

Translational research around Professor Zabel and Professor Dalhoff focuses on clinical trials on COPD as well as asthma and pneumonia aiming at the evaluation of therapeutic options in context of infection and inflammation. Their studies on COPD have brought up results on clinical impact of different treatment schemes as well as insights into the impact of innate immunity with regard to pathogen recognition in the lungs. The suggestion that persistent infection with pathogens such as *C. pneumonia* and *H. influenzae* is suggested to be involved in chronic lung diseases, such as COPD, is only one of many examples for the interrelation of scientific activities among Z.I.E.L's branches, that benefit from a common platform for scientific exchange provided by the center.

Selected Partners

CAPNETZ Foundation; University of Maastricht; Charité Universitätsmedizin Berlin: Department for Infectiology and Pneumology; Research Center Borstel: Experimental Pathology; Hamburg University of Technology: Institute of Medical Technology.

Website www.uksh.de/Med3_Luebeck

Image: *Pneumonia X-Ray photograph*

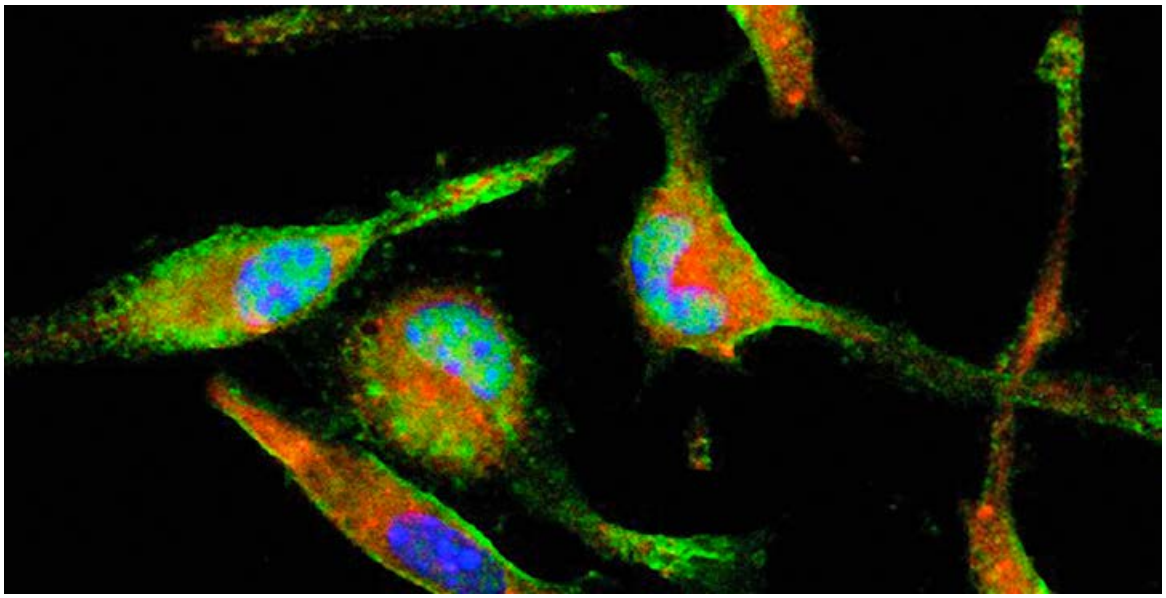
P. Zabel, K. Dalhoff

Publication Highlights

Karsten J, Krabbe K, Heinze H, Dalhoff K, Meier T, Drömann D. Bedside monitoring of ventilation distribution and alveolar inflammation in community-acquired pneumonia. J Clin Monit Comput. 2014 Aug;28(4):403-8.

Rotta Detto Loria J, Rohmann K, Droemann D, Kujath P, Rupp J, Goldmann T, Dalhoff K. Nontypeable Haemophilus Influenzae Infection Upregulates the NLRP3 Inflammasome and Leads to Caspase-1-Dependent Secretion of Interleukin-1β – A Possible Pathway of Exacerbations in COPD. PLoS One. 2013 Jun 26;8(6):e66818.

Drömann D, Rupp J, Rohmann K, Osbahr S, Ulmer AJ, Marwitz S, Röschmann K, Abdullah M, Schultz H, Vollmer E, Zabel P, Dalhoff K, Goldmann T. The TGF-beta-pseudoreceptor BAMBI is strongly expressed in COPD lungs and regulated by nontypeable Haemophilus influenzae. Respir Res. 2010;11:67.



Immune Response 11.3

Innate Immunity 11.3.1

J. Köhl

An example for Z.I.E.L's research on innate immunity can be found in Luebeck's Institute for Systemic Inflammation Research, headed by Professor Jörg Köhl. His laboratory focuses on regulatory networks between the complement system and other parts of innate as well as of adaptive immunity. Within the complement system, the focus is on the anaphylatoxins C3a and C5a, the small cleavage fragments of C3 and C5 that are either generated in response to systemic complement activation through one of the three pathways or locally in immune cells.

In the past, his team has uncovered bi-directional cross-talk between anaphylatoxin receptors with IgG Fc receptors that regulates the inflammatory response in immune complex-mediated inflammation in the skin, lung and the peritoneum. Further, they described intense cross-talk between the anaphylatoxin receptors and Toll-like receptors (TLR) that affect the development of protective, adaptive immune responses in parasitic infection, sepsis and autoimmunity. More mechanistically, his laboratory discovered that such cross between the C5a / C5aR axes and TLRs regulate the maturation and activation of different subsets of dendritic cells in the lung, thereby modulating the induction of maladaptive Th2 and Th17 immunity in allergic asthma. Finally, his team generated the first floxed-GFP C5aR1 knock-in mouse that was instrumental to delineated C5aR1 expression in immune and tissue resident cells and to conditionally knock-out the C5aR1 in lysozyme M-expressing neutrophils, monocytes and macrophages.

In addition to C5aR1, the Köhl laboratory has also generated the first floxed C3aR and floxed C5aR2 tdTomato reporter mice. Such mice will allow to define C3aR and C5aR2 expression under steady state and inflammatory conditions and to conditionally delete these receptors in defined target cells.

Image: *Murine peritoneal macrophages after adhesion to plastic surface. Shown is the expression of the macrophage marker F4/80 (green) and acidic cell organelles (red). The cell nuclei stain blue (DAPI).*

Publication Highlights

Strait RT, Posgai MT, Mahler A, Barasa N, Jacob CO, Köhl J, Ehlers M, Stringer K, Shanmukappa SH, Witte D, Hossain M, Khodoun M, Herr AB, Finkelman FD. **IgG1 protects against renal disease in a mouse model of cryoglobulinemia**. 2015 Nature 517:501-504.

Karsten CM, Laumonnier Y, Eurich B, Ender F, Bröker K, Roy S, Czabanska A, Vollbrandt T, Figge J, Köhl J. **Monitoring and cell-specific deletion of C5aR1 using a novel floxed GFP-C5aR1 reporter knock-in mouse**. 2015 J. Immunol. 194:1841-1855.

Engelke C, Wiese A, Schmudde I, Ender F, Ströver HA, Vollbrandt T, König P, Laumonnier Y, Köhl J. **Distinct roles of the anaphylatoxins C3a and C5a in dendritic cell-mediated allergic asthma**. 2014 J. Immunol 193: 5387-5401.

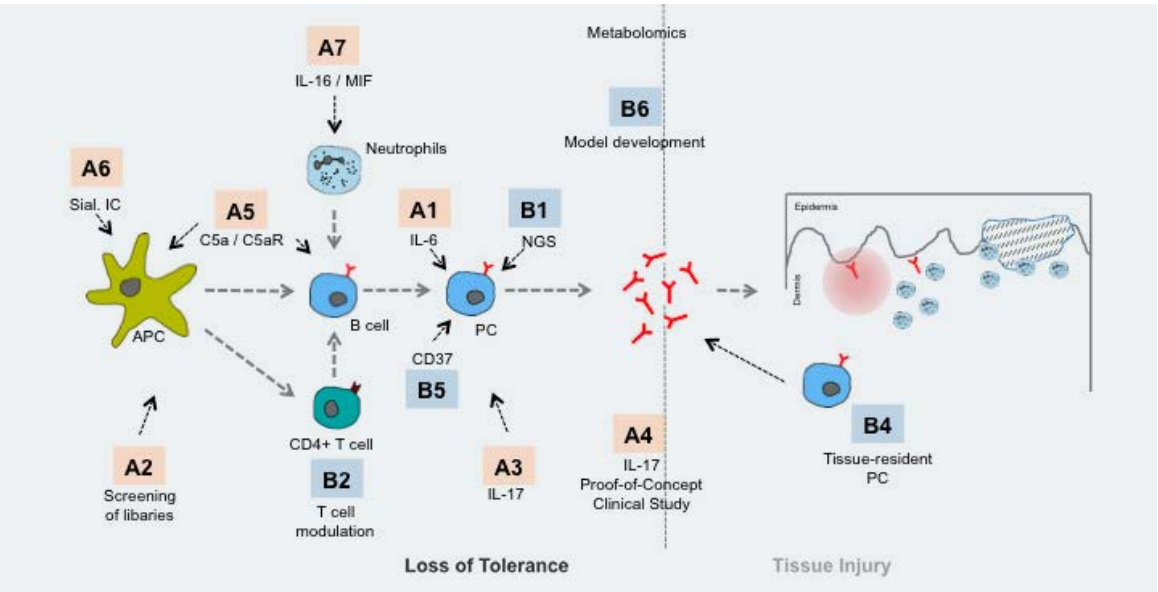
Schmitz V, Almeida LN, Svensjö E, Monteiro AC, Köhl J, Scharfstein J. **C5a and bradykinin receptor cross-talk regulates innate and adaptive immunity in Trypanosoma cruzi infection**. 2014 J. Immunol. 1993:3613-3623.

Karsten CM, Pandey MK, Figge J, Kilchenstein R, Taylor PR, Rosas M, McDonald JU, Orr SJ, Berger M, Petzold D, Blanchard V, Winkler A, Hess C, Reid DM, Majoul IV, Strait RT, Harris NL, Köhl G, Wex E, Ludwig R, Zillikens D, Nimmerjahn F, Finkelman FD, Brown GD, Ehlers M, Köhl J. **Galactosylated IgG1 links FcgRIIB and Dectin-1 to block complement-mediated inflammation**. 2012 Nat. Med. 18:1401-1406.

Selected Partners

Institute of Anatomy; Lübeck Institute of Experimental Dermatology; Institute for Medical Microbiology and Hygiene (since Oct 2015: Department of Infectious Diseases and Microbiology); Cincinnati Children's Hospital, Division of Immunobiology (USA); University of Rio de Janeiro (Brazil).

Website www.isef.uni-luebeck.de | www.irtg1911.uni-luebeck.de



Autoimmunity I 11.3.2

Autoimmunity has developed into a major branch of Z.I.E.L's scientific profile. An example for results with international visibility and in combination with a concept for therapeutic translation can be found at the Clinic of Dermatology, where autoimmunity is scrutinized with regard to blistering skin diseases. Results that give insights into autoimmunity in general have been generated in cooperation with partners from the Institutes for Anatomy, Systemic Inflammation Research, Microbiology, the Research Center Borstel, and many more.

The close link between the clinical care of patients with autoimmune blistering diseases as in-patients (in the Clinic of Dermatology) and out-patients (in the Comprehensive Center for Inflammation Medicine, CCIM) with routine autoimmune laboratory of the Clinic of Dermatology, the Cluster Laboratory "Human Immunophenotyping", and Lübeck's Institute for Experimental Dermatology (LIED) has cumulated in a national and international focus point for the treatment and diagnosis of these diseases and forms the largest research platform for pemphigoid diseases worldwide. To further foster this development

D. Zillikens

the Center for Autoimmune Blistering Diseases Research (CAIBR) has been established under the roof of Z.I.E.L in 2014.

The fruitful long-standing cooperation with the company EUROIMMUN on the development of novel test systems for autoimmune blistering dermatoses has led to the establishment of an endowed professorship on the *Diagnosis of Inflammatory Dermatoses* at LIED. The clinical and research activities on autoimmune blistering diseases and autoimmunity between the University of Luebeck and the Research Center Borstel have cumulated in the second funding period of the DFG funded Research Training Group 1727 *Modulation of Autoimmunity* and the award of the Clinical Research Unit 303 *Pemphigoid Diseases: Molecular Pathways and their therapeutic potential* in 2015.

Image: *Immune cell interactions*

Publication Highlights

Recke A, Vidarsson G, Ludwig R, Freitag M, Möller S, Vonthein R, Schellenberger J, Haase O, Görg S, Nebel A, Flachsbart F, Schreiber S, Lieb W, Gläser R, Benoit S, Sárdy M, Eming R, Hertl M, Zillikens D, König I, Schmidt E, Ibrahim S, and the German AIBD Genetic Study Group. **Allelic and copy-number variations of FcγRs affect granulocyte function and susceptibility for autoimmune blistering diseases**. J Autoimmun. 2015 Jul;61:36-44.

Schmidt E, Zillikens D. **Pemphigoid diseases**. Lancet 2013, 381: 320-32.

Ludwig R, Kalies K, Köhl J, Zillikens D, Schmidt E. **Emerging treatments for pemphigoid diseases**. Trends Mol Med 2013, 19: 501-12.

Spindler V, Rötzer V, Dehner C, Kempf B, Gliem M, Hartlieb E, Harms GS, Schmidt E, Waschke J. **Tandem peptide blocks pemphigus vulgaris skin blistering in mice by preventing loss of desmoglein 3 binding and p38MAPK activation**. J Clin Invest 2013, 123: 800-811.

Srinivas G, Möller S, Wang J, Künzel S, Zillikens D, Baines JF, Ibrahim SM. **Genome-wide mapping of gene-microbiota interactions in susceptibility to autoimmune skin blistering**. Nat Commun. 2013; 4:2462.

Website www.derma.uni-luebeck.de/Forschung/Ansprechpartner.html

Autoimmunity II 11.3.3

The Lübeck Institute of Experimental Dermatology (LIED) was founded in 2014 to bundle research efforts in cutaneous autoimmunity. The funding from the Excellence Cluster Inflammation at Interfaces was the basis for the formation of LIED, as all three directors (Saleh Ibrahim, Ralf Ludwig and Enno Schmidt), have been recruited as professors within the Excellence Cluster.



S. M. Ibrahim, R. Ludwig, E. Schmidt

The research within LIED focuses on 3 major fields: (i) Genetics of cutaneous inflammation, (ii) model systems of inflammatory skin diseases and (iii) translational research in cutaneous autoimmunity.

The clinical and research activities on autoimmune blistering diseases and autoimmunity between the University of Luebeck and the Research Center Borstel have cumulated in the second funding period of the DFG funded Research Training Group 1727 *Modulation of Autoimmunity*, the Research Training Group *Genes, Environment and Inflammation* and a significant contribution to the recently established Clinical Research Unit 303 *Pemphigoid Diseases: Molecular Pathways and their therapeutic potential* in 2015.

Publication Highlights

Recke A, Vidarsson G, Ludwig R, Freitag M, Möller S, Vonthein R, Schellenberger J, Haase O, Görg S, Nebel A, Flachsbart F, Schreiber S, Lieb W, Gläser R, Benoit S, Sárdy M, Eming R, Hertl M, Zillikens D, König I, Schmidt E, Ibrahim S, and the German AIBD Genetic Study Group. **Allelic and copy-number variations of FcγRs affect granulocyte function and susceptibility for autoimmune blistering diseases**. J Autoimmun. 2015 Jul;61:36-44.

Schmidt E, Zillikens D. **Pemphigoid diseases**. Lancet 2013, 381: 320-32.

Ludwig R, Kalies K, Köhl J, Zillikens D, Schmidt E. **Emerging treatments for pemphigoid diseases**. Trends Mol Med 2013, 19: 501-12.

Spindler V, Rötzer V, Dehner C, Kempf B, Gliem M, Hartlieb E, Harms GS, Schmidt E, Waschke J. **Tandem peptide blocks pemphigus vulgaris skin blistering in mice by preventing loss of desmoglein 3 binding and p38MAPK activation**. J Clin Invest 2013, 123: 800-811.

Srinivas G, Möller S, Wang J, Künzel S, Zillikens D, Baines JF, Ibrahim SM. **Genome-wide mapping of gene-microbiota interactions in susceptibility to autoimmune skin blistering**. Nat Commun. 2013; 4:2462.

Website www.lied.uni-luebeck.de

II.3.4 Autoimmunity III

Another field of inflammation with regard to autoimmunity is represented by Prof. Riemekasten's rheumatological research on phenomena stimulating autoantibodies against G protein coupled receptors of systemic sclerosis and other connective tissue diseases. Her team was recruited to Luebeck in 2015 and their projects aim at understanding the therapeutic potential of regulatory T cells and disbalances and autoantibody activities in the context of systemic autoimmune diseases such as systemic sclerosis and Systemic Lupus erythematosus (SLE). Her liaison group with the Research Center Borstel will develop mouse models for autoimmune diseases together with Xinhua Yu.

In addition to basic research on pathogenic mechanisms of autoimmune diseases her group developed the concept of low-dose IL-2 therapy for the treatment of SLE in order to strengthen regulatory T cells and thus to restore immunological tolerance. This concept was recently translated into the clinic and is currently tested in a phase I / IIa clinical trial addressing the safety, tolerability, immunological and clinical responses and the clinical efficacy of a subcutaneous low-dose IL-2 therapy in patients with refractory SLE (PRO-IMMUN).

G. Riemekasten, P. Lamprecht

Research of the Clinical Research Unit 170 "Early pathogenesis of granulomatosis with polyangiitis (GPA)" is coordinated by Prof. Peter Lamprecht. The CRU170 focuses on chronic inflammation and break of tolerance, formation of ectopic lymphatic structures, autoantibody-production by tissue-resident plasma cells and alterations of the T-cell response in GPA. The group participates in the RTG1727 "Modulation of Autoimmunity" and EXC306 "Inflammation at Interfaces". The Vasculitis Center UKSH is also headed by Prof. Lamprecht. In this Center clinicians and scientists collaborate in order to coordinate their clinical and scientific activities focusing on vasculitis research.

Publication Highlights

Millet A, Martin KR, Bonnefoy F, Saas P, Mocek J, Alkan M, Terrier B, Kerstein A, Tamassia N, Satyanarayanan SK, Ariel A, Ribeil JA, Guillevin L, Cassatella MA, Mueller A, Thieblemont N, Lamprecht P, Mouthon L, Perruche S, Witko-Sarsat V. **Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis.** J Clin Invest 2015;125:4107-21.

von Spee-Mayer C, Siegert E, Abdirama D, Rose A, Klaus A, Alexander T, Enghard P, Sawitzki B, Hiepe F, Radbruch A, Burmester GR, Riemekasten G, Humrich JY. **Low-dose interleukin-2 selectively corrects regulatory T cell defects in patients with systemic lupus erythematosus.** Ann Rheum Dis. 2015 Aug 31. pii: annrheumdis-2015-207776.

Becker MO, Kill A, Kutsche M, Guenther J, Rose A, Tabeling C, Witzenrath M, Kühl AA, Heidecke H, Ghofrani HA, Tiede H, Schermuly RT, Nickel N, Hoeper MM, Lukitsch I, Gollasch M, Kuebler WM, Bock S, Burmester GR, Dragun D, Riemekasten G. **Vascular receptor autoantibodies in pulmonary arterial hypertension associated with systemic sclerosis.** Am J Respir Crit Care Med. 2014 Oct 1;190(7):808-17.

Enghard P, Rieder C, Kopetschke K, Klocke JR, Undeutsch R, Biesen R, Dragun D, Gollasch M, Schneider U, Aupperle K, Humrich JY, Hiepe F, Backhaus M, Radbruch AH, Burmester GR, Riemekasten G. **Urinary CD4 T cells identify SLE patients with proliferative lupus nephritis and can be used to monitor treatment response.** Ann Rheum Dis. 2014 Jan;73(1):277-83.

Selected Partners

Prof. Burmester, Charité Universitätsmedizin Berlin; Prof. A. Radbruch, DRFZ, Berlin; CellTrend GmbH, Luckenwalde.

Website www.uksh.de/rheuma-luebeck

Respiratory and Allergic Diseases II.3.5

Research on inflammatory processes during respiratory diseases has created a starting point within Z.I.E.L's increasing activities for the combination of investigating lung specific mechanisms and allergy phenomena in general.

Allergy II.3.5.1

Prof. Jappe started in Lübeck & Borstel in 2010 with both, a clinical focus on Interdisciplinary Allergology and a scientific one on molecular phenotyping. Meanwhile, an Interdisciplinary Allergy-Outpatient Clinic (Prof. Jappe) in cooperation with the Depts. of Dermatology, Pediatrics (Prof. Kopp) and Internal Medicine was established in Lübeck, which is closely associated with the Allergy Outpatient Clinic in the Medical Clinic Borstel and the Research Group Clinical and Molec-ular Allergology in the FZB (Prof. Jappe).



U. Jappe, M. Kopp, H. Fehrenbach (FZB)

At the Research Center Borstel (FZB), the Research Group Clinical and Molecular Allergology is part of the Priority Area Asthma and Allergy (Prof. Fehrenbach) and focuses on inhalant, food and drug allergies as well as on bronchial asthma. Main aspects are the isolation, identification and structural characterization of allergens in order to improve allergy diagnostic tests and to use them as tools for investigating the influence of allergen structures, for example, on sensitization routes, allergy and asthma pathomechanisms, and on the severity and localization (organ involvement) of the individual allergic symptom development.

It was possible to identify, isolate and characterize novel allergens from well-known and relevant allergen sources, like lipophilic peanut and house dust mite allergens. We developed a novel strategy for the isolation and purification of peanut defensins and oil proteins (oleolysins). Defensins and oleosins have been officially accepted as new allergens by the WHO / IUIS Allergen Nomenclature Subcommittee.

Publication Highlights

Homann A, Röckendorf N, Kromminga A, Frey A, Jappe U. **Immunogenic Infliximab Epitopes located in TNF-alpha Binding Regions with No Cross-Reactivity to Adalimumab**. Journal of Translational Medicine 2015.

Jappe U, Nikolic J, Opitz A, Homann A, Zabel P, Gavrovic-Jankulovic M. **Apparent IgE-negative anaphylactic reaction to banana combined with kiwi-allergy – Complementary diagnostic value of purified single banana allergens**. Journal of the European Academy of Dermatology and Venereology 2015; Mar 31.

Schwager C, Kull S, Krause S, Schocker F, Petersen A, Becker WM, Jappe U. **Development of a Novel Strategy to Isolate Lipophilic Allergens (Oleosins) from Peanuts**. PLoS ONE 2015, Bd 10, Nr. 4, S. e0123419.

Petersen A, Kull S, Rennert S, Becker W-M, Krause S, Ernst M, Gutsmann T, Bauer J, Lindner B, Jappe U. **Peanut defensins: novel allergens isolated from lipophilic peanut extract**. J Allergy Clin Immunol. 2015 Nov;136(5):1295-301.e1-5.

Petersen A, Rennert S, Kull S, Becker WM, Notbohm H, Goldmann T, Jappe U. **Roasting and lipid binding provide allergenic and proteolytic stability to the peanut allergen Ara h 8**. Biol Chem. 2014 Feb;395(2):239-50.

Selected Partners

University of Virginia Asthma and Allergic Diseases Center, University of Virginia Health System, Charlottesville, USA; Department of Biochemistry, Faculty of Chemistry, University of Belgrade, Belgrade, Serbia; Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland; Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, University of Wien; Department of Engineering – Biotechnology, Aarhus University, Aarhus, Denmark.

Website www.fz-borstel.de/cms/de/forschungszentrum/programmbereich-asthma-u-allergie/klinische-und-molekulare-allergologie/mitarbeiter.html

Molecular Pathways 11.4

Chronophysiology 11.4.1

The rotation of the Earth around its axis creates a recurring succession of day and night with a period of 24 hours. Inherently connected to the light-dark changes ("Zeitgeber") in environmental conditions, genetically encoded circadian (Lat. *circa diem* – about a day) cellular clocks help to optimally adapt physiology and behavior to these rhythms.

H. Oster, W. Solbach

Professor Oster's team investigates clock gene impact on physiological rhythms while Professor Solbach's group focuses on the immunological impact of clock regulation in the context of T-cell function. Together both groups analyze the interaction of sleep and immune cell clocks in the regulation of autoimmune processes in the brain. This project is part of the DFG-funded Collaborative Research Unit (SFB-654) "Sleep & Plasticity".

Previous studies from the two groups have established and characterized molecular clocks based on transcriptional-translational feedback loops in human and murine T-cells. Ongoing experiments focus on how circadian clocks in different tissues are aligned with external time. Moreover, using a mouse model of experimental auto-immune encephalomyelitis (EAE), the team studies the impact of T-cell clock function on the regulation of autoimmune processes. Unpublished data show that, in EAE mice, the timing of immunization predicts disease outcome and this dependence is lost in mice with genetic deletion of clock function in T-cells. Tissue clock function appears to control T-cell trafficking, which may underlie the observed diurnal variation in autoimmune responses.

Circadian clocks control tissue physiology via transcriptional programs involving hundreds of cell-type specific genes. Using RNA microarray analyses the team analyzes the molecular basis of circadian auto-immune regulation, aiming at identifying potential targets for chronotherapeutic interventions.

Publication Highlights

Bollinger T, Bollinger A, Gies S, Feldhoff L, Solbach W, Rupp J. **Transcription regulates HIF-1α expression in CD4(+) T cells**. Immunol Cell Biol. 2016 Jan;94(1):109-13.

Husse J, Eichele G, Oster H. **Synchronization of the mammalian circadian timing system: Light can control peripheral clocks independently of the SCN clock: Alternate routes of entrainment optimize the alignment of the body's circadian clock network with external time**. Bioessays. 2015 Oct;37(10):1119-28.

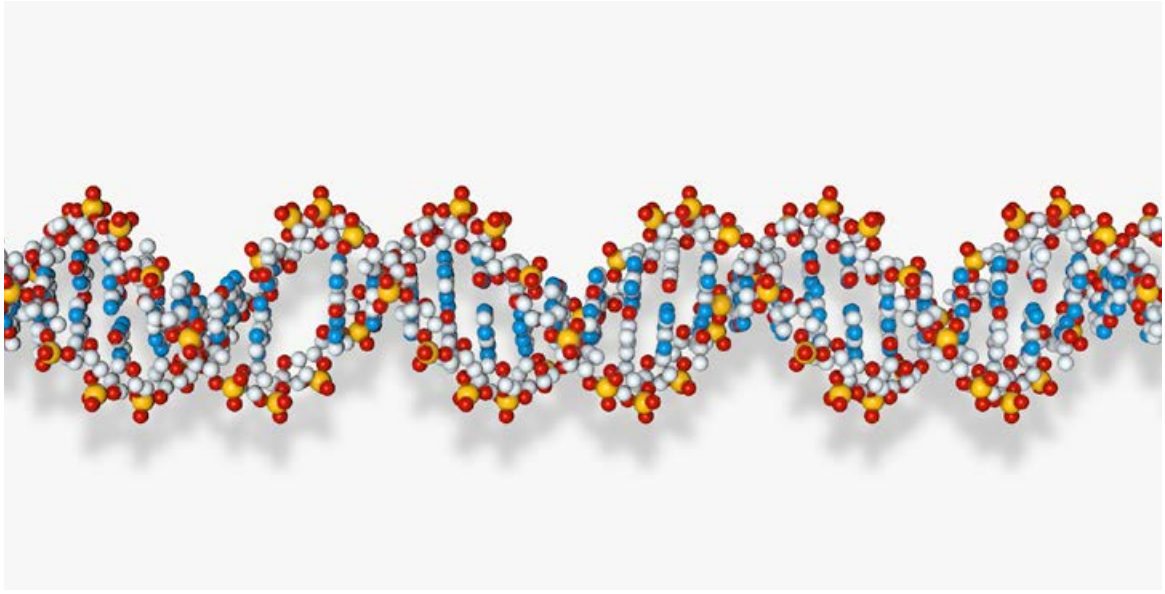
Husse J, Leliavski A, Tsang AH, Oster H, Eichele G. **The light-dark cycle controls peripheral rhythmicity in mice with a genetically ablated suprachiasmatic nucleus clock**. FASEB J. 2014 Nov;28(11):4950-60.

Bollinger T, Leutz A, Leliavski A, Skrum L, Kovac J, Bonacina L, Benedict C, Lange T, Westermann J, Oster H, Solbach W. **Circadian clocks in mouse and human CD4+ T cells**. PLoS One. 2011;6(12):e29801.

Selected Partners

Ludwig-Maximilian University, Munich, Germany;
Max-Planck Institute for Biophysical Chemistry, Göttingen, Germany.

Website www.chronophysiologie.uni-luebeck.de



Functional Genomics II.4.2

Chronic inflammatory diseases result from the interaction of genetic and environmental triggers like infectious, chemical, physical, nutritional, and behavioral factors. While major progress has been made in identifying genetic susceptibility factors, comparatively little is known about environmental risk factors or the forces that lead to variation in genetic susceptibility in nature. Microbial cells are estimated to outnumber human cells by a factor of ten to one. Recent advances in the field of metagenomics have begun to define these microbial communities, but knowledge of their influence on immunity and susceptibility to disease remains in its infancy. Important questions remain regarding the extent to which the microbiota is influenced by genetic variation in the host genome and whether disease susceptibility may be mediated by the microbiota. Indirect evidence (*i.e.* cellular fatty acid profiles of the fecal bacteria) suggests a prominent role of host genetic background on the composition of the microbiota, and in fostering a communicable, pro-inflammatory microbiota.

We are examining the hypothesis that naturally occurring variation in the host genome influences the composition of the resident microbiota, and this in turn influences susceptibility to chronic inflammatory diseases. To test this hypothesis we are using a systems genetic approach and unique mouse models of skin inflammatory diseases.

S. M. Ibrahim, J. Erdmann

An example of the functional genomics studies within Z.I.E.L is the work of the genetics of skin inflammation research group. The group is focusing to identify and functionally validate susceptibility genes for skin inflammatory diseases e.g. autoimmune blistering diseases, cutaneous lupus and psoriasis in large cohorts.. The cohorts recruited by the International Autoimmune Blistering Diseases (AIBD) Genetics consortium are the basis for ongoing studies aiming at identifying AIBD risk genes and perform gene-environment interaction studies (e.g. microbiota, smoking). Recently, the group contributed to landmark studies identifying st18 as the first pemphigus vulgaris disease gene and FcγRs copy numbers variations as a major contributor to Bullous pemphigoid disease susceptibility. The group also coordinated the first genome wide association study in cutaneous lupus.

Publication Highlights

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Selected Partners

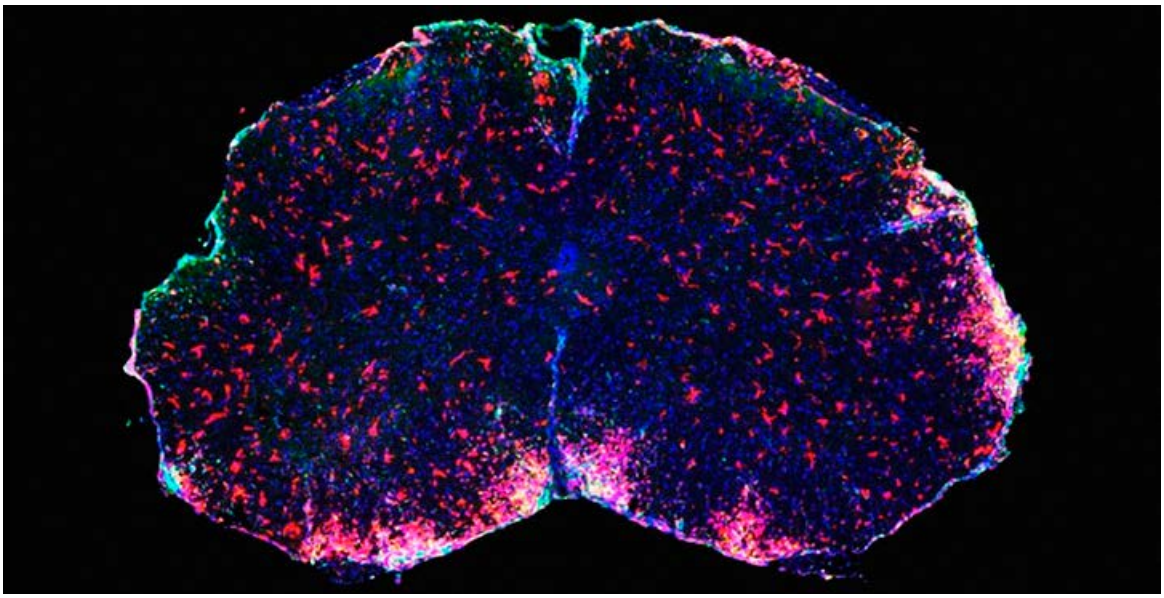
Max Planck Institute for Evolutionary Biology, Plön, Germany.
AIBD Genetics International Consortium; Popgen Database, Kiel, Germany.

Websites www.lied.uni-luebeck.de | www.iieg.uni-luebeck.de

III Z.I.E.L Translational Concept: Diagnosis, Therapy and Intervention

Researchers in Z.I.E.L are devoted to transfer knowledge and expertise from basic research to clinical application.

This has led to the formation of efficient structures in which pre-clinical research and clinical applications closely interact.



III.1 Mouse Models

Murine models of inflammation at epithelial interfaces play important roles for the functional understanding of disease mechanisms. Within the Z.I.E.L, the cluster laboratory (CL) XII of the excellence cluster I@I has formed an integrated research structure that is open for all members of the Z.I.E.L The overarching goal of this CL is to provide the infrastructure and experimental disease models. With regard to this goal, we have defined the following aims:

- Develop SOPs for experimental models of selected barrier diseases
- Setup "immune evaluation" strategies for genetically-altered mouse lines
- Provide genetic services for genetically-altered mouse lines.
- Implement data management infrastructure for genetically-altered mouse lines and available experimental models of selected barrier diseases.

The CL serves as partner of the university in implementing long-term plans to modernize and reorganize the animal housing capacities.

III.1.1 Cellular Phenotyping

Cellular Phenotyping is done with two cell sorters, one cell analyzer and one confocal microscope. This facility is open to all Z.I.E.L members and is regularly used for cell analysis in the mouse models and projects outlined below:

- Allergic asthma (OVA, house dust mite, dendritic cells adoptive transfer)
- Food allergy
- Passive anaphylaxis
- Different models of skin blistering diseases (active / passive)
- Autoimmunity advanced intercross lines
- mtDNA mutant mice (conplastic strains)
- Spontaneous lupus (NZM2410)
- Spontaneous autoimmune pancreatitis
- Infectious disease models (Toxoplasma, Trypanosoma, Leishmania, Chlamydia, Histoplasma, *Mycobaterium tuberculosis*)

J. Köhl

Image: *DMF is a new multiple sclerosis drug. The illustration shows a section of mouse spinal cord under a fluorescence microscope. DMF works on the immune cells (red), which are responsible for damaging the nerve fibres. Cell nuclei appear as blue.*

In addition to such models, we have established phenotypic and functional immune evaluation strategies including:

- Differentiation and purification of DC subsets, macrophages, eosinophils, neutrophils and T cell subsets from lung, small intestine and secondary lymphoid organs
- In vitro differentiation of Th1 cells subsets (Th1, Th2, Th17, Treg)
- Determination of intracellular cytokine production in DCs and $CD4^+$ Th cells
- Adoptive transfer of antigen-pulsed primary DCs and Myeloid suppressor cells
- Adoptive transfer of CD4+ Th cells
- Assessment of allergen uptake by DCs, macrophages and eosinophils in vitro and in vivo
- DC/T cell co-culture experiments → cytokine profiling

Publication Highlights

Strait RT, Posgai MT, Mahler A, Barasa N, Jacob CO, Köhl J, Ehlers M, Stringer K, Shanmukappa SH, Witte D, Hossain M, Khodoun M, Herr AB, Finkelman FD. IgG1 protects against renal disease in a mouse model of cryoglobulinemia. 2015 Nature 517:501-504.

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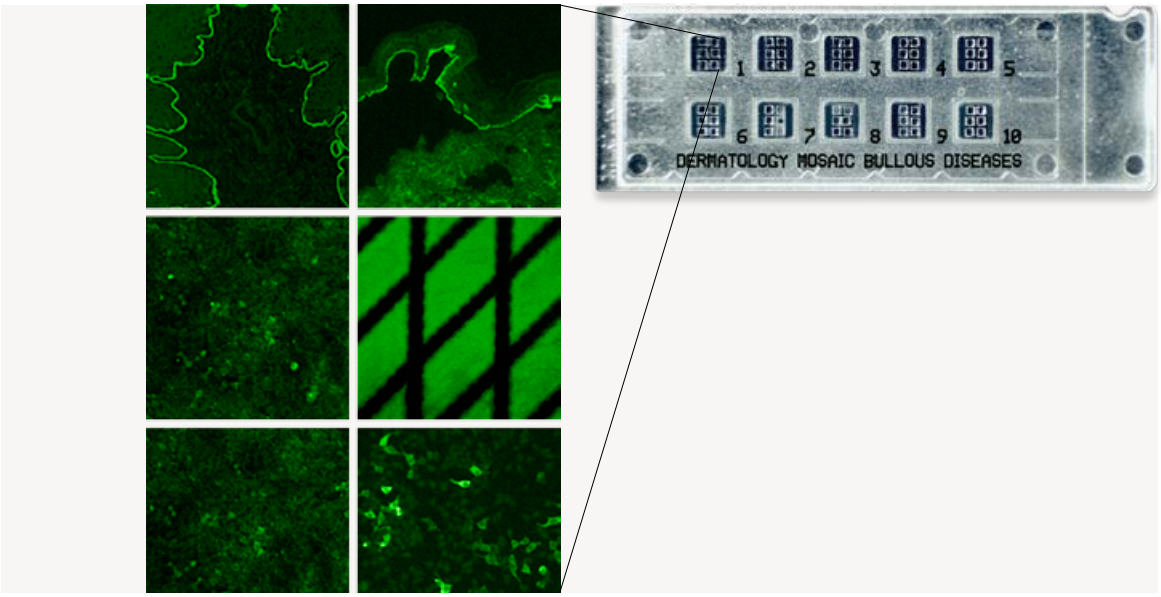
Karsten CM, Pandey MK, Figge J, Kilchenstein R, Taylor PR, Rosas M, McDonald JU, Orr SJ, Berger M, Petzold D, Blanchard V, Winkler A, Hess C, Reid DM, Majoul IV, Strait RT, Harris NL, Köhl G, Wex E, Ludwig R, Zillikens D, Nimmerjahn F, Finkelman FD, Brown GD, Ehlers M, Köhl J. Galactosylated IgG1 links FcRIIB and Dectin-1 to block complement-mediated inflammation. 2012 Nat. Med. 18:1401-1406.

Selected Partners

Institute of Pharmacology; Institute of Anatomy; Department of Dermatology; Department of Infectious Diseases and Microbiology; Institute of Systemic Inflammation Research; Medical Dept. I; Medical Dept. II.

Websites inflammation-at-interfaces.de/de/forschung/forschungsgebiete/cluster-labore/cl-xii
www.isef.uni-luebeck.de/canacore



III.1.2 Genotyping

The Z.I.E.L groups developed a large numbers of unique mouse models to study different aspects of chronic inflammation and infection. One example are the Lübeck 'conplastic' strains. The Ibrahim group generated 24 individual strains carrying single point mutations in their mitochondrial genome. These strains are ideal to study the role of mitochondrial genome polymorphism / mutations that have been linked to longevity and age-related diseases. The strains have been used by at least 15 research groups to study different aspects of inflammation and metabolic diseases. The same group also developed another unique resource, the autoimmune advanced intercross line, that were used by them and by others to identify chronic inflammation disease genes.

S. M. Ibrahim

Finally, the CL has established genetic services such as quantitative trait locus (QTL) mapping (MEGA-MUGA Illumina array), Marker-assisted backcrossing (f speed congenics; microsatellite, SNP, Illumina arrays), Genetic quality control (Illumina array, Affymetrix diversity array, SNP markers) and rRNA-based gut and skin microbiota analysis.

Publication Highlights

Bischof J, Müller S, Borufka L, Asghari F, Möller S, Holzhüter SA, Nizze H, Ibrahim SM, Jaster R. Quantitative Trait Locus Analysis Implicates CD4+ / CD44high Memory T Cells in the Pathogenesis of Murine Autoimmune Pancreatitis. PLoS One. 2015 Sep 1;10(9):e0136298.

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Website www.lied.uni-luebeck.de

Image: *Biomarkers for bullous skin diseases*

Comprehensive Center for Inflammation Medicine (CCIM) III.2

The Comprehensive Center for Inflammation Medicine significantly contributes to clinical research and extended phenotyping. It offers clinical research support for cohort studies to members of all research areas within the Cluster. Moreover, through interdisciplinary conferences and outpatient clinics for chronic inflammatory diseases, it contributes to the integration of diverse research areas within the Cluster and with the university clinics. The CCIM is the major source of biosamples, allowing the cluster to analyze the similarity as well as the differences between related diseases. The patient cohorts provided by the CCIMs are crucial for the verification of hypotheses and for the identification of new therapeutic targets which can be translated into clinical practice. CCIM provides also the frame for developing its own diagnostic and therapeutic strategies, patient reported outcome and efficacy of new therapeutic options.

Despite the expansion in the number of "biologic" therapies, which are available for the treatment of psoriasis, the identification of biomarkers associated with response to treatment is an unmet clinical need.

D. Thaçi

Focusing on TNF-alpha, IL-12/23 and interleukin 17 antagonists, our investigations aim to identify genetic predictors of response to targeted therapy in psoriasis patients via a combined gene association and gene expression analysis. In addition to genetic factors influencing treatment response, the cutaneous microbial flora will be determined both prior to-, and during targeted treatment with biologics. Combining these genetic and environmental approaches gives promise to identify novel biomarkers of direct translational relevance.

Clinical members of CCM meet weekly in an "Inflammation Board" to discuss diagnostic and therapeutic strategies for patients with autoimmune diseases.

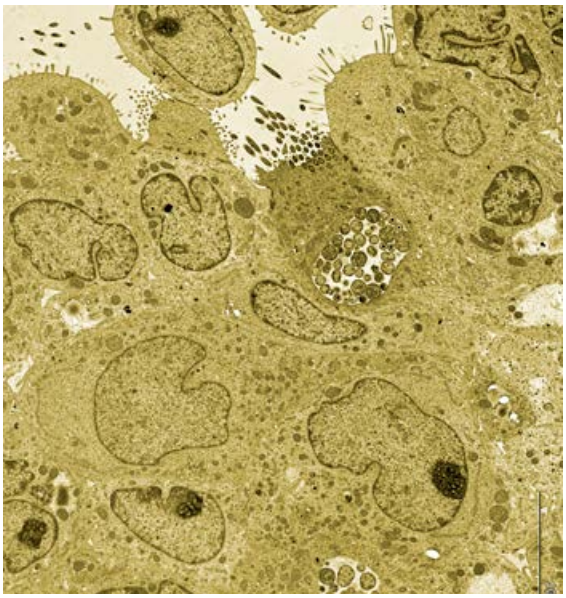
III.3 Comprehensive Center for Infectious Diseases (CCINF)

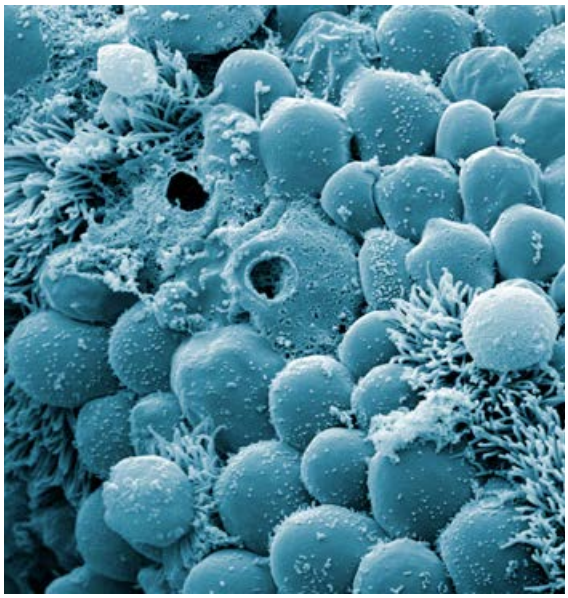
J. Rupp

Within the newly formed Department of Infectious Diseases and Microbiology (DIDM) outpatient and hospitalized patients with all kind of infections are cared for. Whereas a particular focus in the outpatients is HIV infection, two major branches are followed with respect to hospitalized patients. On the clinical ward mostly patients suffering from classical infectious diseases like pneumonia, urogenital tract infections, bacteremia, soft skin and tissue infections and patients with multi-resistant pathogens are treated. Campus-wide we are taking care about patients in different clinical disciplines with organ-specific sequelae that require e.g. surgical interventions, to optimize diagnostic procedures and treatment strategies. Based on the broad spectrum of patients seen by the ID physicians, the DIDM takes part in a multitude of IITs and clinical trials in the field of infectious diseases.

The Department of Infectious Diseases and Microbiology is part of the BMBF-funded German Research Center of Infectious Research (DZIF). Together with the DZIF-partner sites several IITs on important infectious diseases but also with regard to pathogen surveillance and epidemiology have been started in Lübeck. Current studies include the molecular characterization of Influenza A virus during a two year observational period. Another study deals with the characterization of the microbiota of hospitalized patients for defining risk factors in acquiring necrotizing enterocolitis by *C. difficile*. Further studies are planned in the surveillance of multidrug- resistant organisms (MDRO), including VRE, MRSA, ESBL and 4MRGN, particularly Carbapenem-resistant *Acinetobacter sp*. and *Pseudomonas sp*. Within the translational unit of hospital-acquired and antimicrobial-resistent blood stream infections (HAARBI) a particular focus will be given severe bloodstream infections. With regard to chlamydial infections a local cohort study including fertile females and women suffering from infectious infertility has been started in 2013 and is currently expanded for a multi-centre study to obtain data on microbiota-related changes on the detection of STDs in infertile females.

The CCINF is the weekly meeting point for all clinicians to discuss optimal diagnostic and therapeutic modalities for all patients with complicated infections. To expand knowledge of young doctors, a structured rotation program with colleagues at the Medical Clinic at UKE Hamburg and the Research Center Borstel has been initiated in 2015.





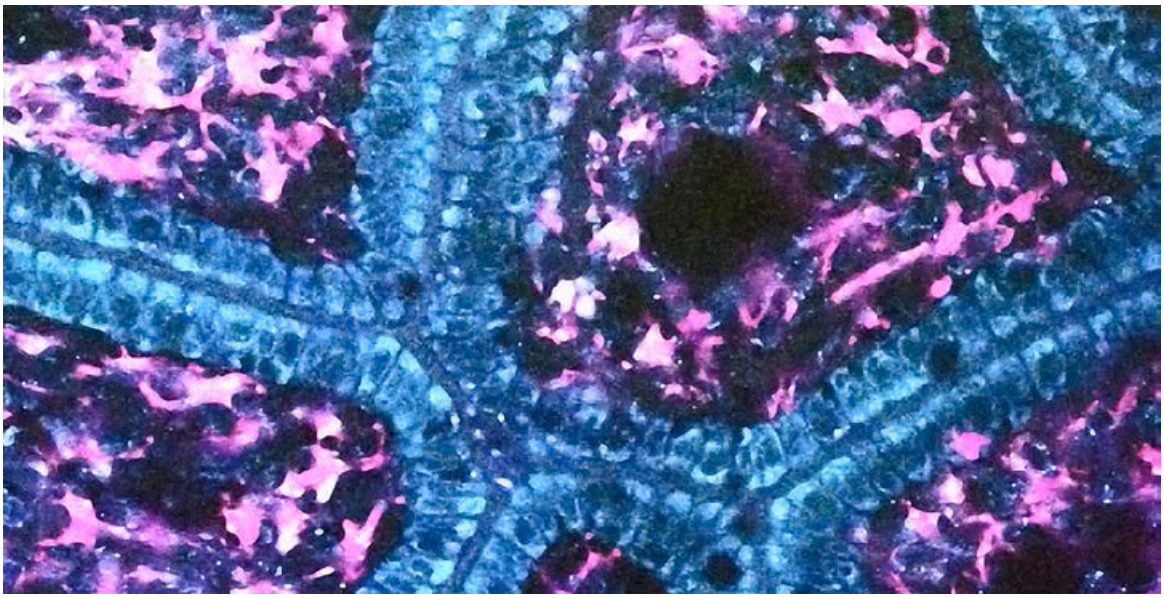
Clinical Tuberculosis Center (ClinTB) III.4

The Clinical Tuberculosis Center (DZIF) at the Research Center Borstel cares for the largest number of patients with MDR-TB and XDR-TB in Germany. Clinicians and researchers of the center coordinate national and international studies as well as capacity building activities at UL partner Universities, UMSF in Chisinau, Moldova and at UNAM in Windhoek, Namibia. Together with CCINF and UKE (Hamburg) the ClinTB has launched a clinical curriculum for Infectious Diseases training in Northern Germany.

C. Lange

Comprehensive Center for Allergic Diseases (CCAD) III.5
[to be established]

Z.I.E.L researchers in Lübeck and Borstel have recognized the necessity to enhance cooperation in order to be able to achieve sustainable and competitive funding. Key institutions involved are, among others, the Institute for Systemic Inflammatory Research, the Clinics for Pediatrics, Rheumatology, Internal Medicine III and ENT. The group is currently in a very vital discussion process for the formation of the CCAD.



III.6 Microscopic Imaging of Inflammatory Processes

In recent years microscopic imaging of the cellular dynamics of immunological processes has greatly improved the understanding of immune reactions. To have access to these technologies in Lübeck, the Institute of Anatomy and the Institute of Biomedical Optics established a cooperation that combines the knowledge of immunology and morphology with knowledge of optical imaging and manipulation. This cooperation was started with two major goals. The first goal was to have access to the latest imaging technologies for the analysis of immune reactions and the second goal was to develop new optical imaging and manipulation techniques for biomedical research. As a result, several advanced microscopes are now run jointly by both institutes and are accessible to other researches. Today, researchers have access to three multiphoton microscopes that are tailored individually for specific imaging and manipulation needs. Besides providing standard spectral multiphoton imaging to track immune cells within tissue and living animals, two microscopes are equipped with long wavelength femtosecond lasers that are allow imaging deeper in the tissue compared to conventional titanium sapphire-femtosecond lasers. Two microscopes are equipped with fluorescence lifetime imaging. This technology allows measuring the metabolic state of cells, is used for markerless fingerprinting of specific cell types, and can be used to image optical sensors that function based on fluorescence resonance energy transfer (FRET). Two microscopes are equipped with custom built systems for laser surgery that can precisely destroy individual cells to follow the epithelium's healing process as well as the immune system's reaction towards small lesions that are thought to occur frequently at mucosal barriers.

Currently, several joint research projects aim to develop new technologies to overcome current limitations of optical imaging. A new approach termed optical coherence microscopy (OCM) developed at the Institute of Biomedical Optics now allows high speed imaging with microscopic resolution to visualize mucus transport in living anaesthetized animals. This technology is currently implemented in endoscopes and provides microscopic morphologic information of mucosal tissues in patients. Another promising approach is to combine OCT with multiphoton microscopy to not only follow specifically labeled immune cells in organs but also to get detailed morphologic information of the tissue.

To increase the accessibility of imaging technology to other researchers on campus, the microscopes will move to a new facility in the cellar of the Center for Brain Behavior and Metabolism (CBBM). This facility will combine advanced optical imaging with various advanced whole animal imaging modalities such as positron emission tomography, single photon

Image: *Multiphoton microscopy of the murine intestine in the living mouse. Autofluorescence imaging is used to show the villus morphology (green). Macrophages are genetically labeled with fluorescent protein (pink).*

emission computed tomography, computer tomography, magnetic resonance tomography and magnetic particle imaging. The facility will be in a biosafety level 2 environment that will allow infection studies with human pathogens. The facility will also have its own animal facility to study animals over extended periods of time. Together with the microscopes, a research group from the Institute of Biomedical Optics will transfer to the CBBM to foster cooperation with biomedical researchers. Consequently, within the upcoming years, new possibilities will open up to drive research at the border between biomedical research and imaging.

Publication Highlights

Klinger A, Krapf L, Orzekowsky-Schroeder R, Koop N, Vogel A, Hüttmann G. **Intravital autofluorescence 2-photon microscopy of murine intestinal mucosa with ultra-broadband femtosecond laser pulse excitation: image quality, photodamage, and inflammation**. J Biomed Opt. 2015 Nov;20(11):116001.

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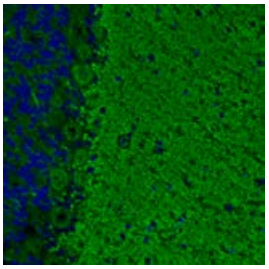
Bermbach S, Weinhold K, Roeder T, Petersen F, Kugler C, Goldmann T, Rupp J, König P. **Mechanisms of cilia-driven transport in the airways in the absence of mucus**. Am J Respir Cell Mol Biol. 2014 Jul;51(1):56-67.



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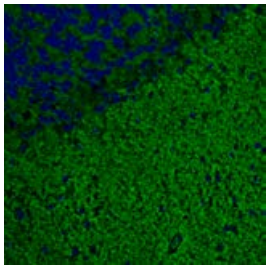

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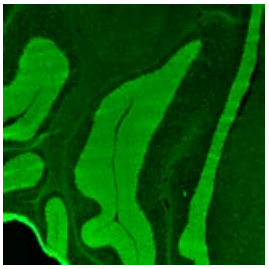

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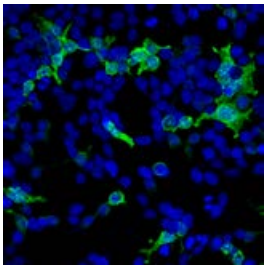


rHEK293 GLURD2

III.7 Biomarkers

Along the translational mission of the Z.I.E.L, it is important to bring research not only to the patient but also to the market. EUROIMMUN is one of the world's leading developers and manufacturers of medical laboratory reagents, in the foreground for the diagnosis of autoimmune and infectious diseases and allergies. The techniques applied are predominantly indirect immunofluorescence, ELISA, immunoblot and microarrays for genetic marker diagnostics. The company's expertise encompasses also the application of the products in reference laboratories which are worldwide unequalled, especially in autoimmune diagnostics. The reference laboratory in Lübeck receives five hundred serum samples daily, from many countries. It helps EUROIMMUN's customers to secure their results.

Among the spectrum of topics, EUROIMMUN is dealing with, the contributions of this institute are of major relevance for Z.I.E.L We identified target antigens of different disease-relevant autoantibodies using histo-immune precipitation techniques, chromatography and mass spectrometry, as formerly CUZD1 and GP-2 (Crohn's disease) and DNA-bound lactoferrin (ulcerative colitis). During the reporting period it was possible to identify 18 neural autoantigens. Among them, for the use as target antigens in immunotests, several patents were applied, based on the identification of ITPR1 (Inositoltriphosphat-Receptor), ATP1A3 (Neuron-specific Na-K-ATPase), NBCe1 (Natriumbicarbonat-Cotransporter), Flotillin and Neurochondrin.

Further projects regard the development of other test antigens, for example, recombinant species specific VlsE and dimeric OspC antigens for the diagnosis of *Borrelia burgdorferi* and, more recently, ZIKA-Virus infections, gliadin peptides (coeliac disease), desmoglein 1 and 3 (pemphigus vulgaris) or thrombospondin (THSD7A) and PLA2R (membranous nephropathy), which are now employed in ELISA and immunoblot systems.

In collaboration with the clinic of dermatology Lübeck, for the treatment of pemphigus vulgaris and bullous pemphigoid, specific adsorbers have been developed using recombinant desmoglein 1 and 3 as well as NC16A, coupled to NHS-activated Sepharose. Using these matrices, pathogenic plasma autoantibodies in pemphigus or bullous pemphigoid could be efficiently and specifically decreased to less than 10 % without influencing the level of total IgG or IgG directed against viral proteins. Clinical trials will follow.

Website www.euroimmun.de

Image: *Antigen detection by high-powered immunofluorescence*

Z.I.E.L Infrastructure IV

IV.1 Research Building and Laboratories

Applied methods in Z.I.E.L's research groups range from X-ray structure analysis, fragment screening in crystals, 12-colour-fluorescence analysis to 2-photon-microscopy. There is a cell sorting core facility as well as a central biobanking project including a registry for a large variety of biomedical samples. A new animal facility has been established in 2014 and there are laboratory units of all security levels, except BSL4.

Z.I.E.L research groups work in a number of different laboratories scattered across the university's campus. The new research building will relocate lab space for inflammatory and infection research with a unifying and highly interdisciplinary whole of 5.000 square meters for its members. In addition to Luebeck's equipment for basic research, imaging and clinical trials. Transdisciplinary research will be fostered, since the CBBM buliding is wall-to-wall, which will lead to high cross-fertilization of ideas. The research site at Leibniz Research Center Borstel provides access to an S3-Laboratory that is used for experimental projects on infections in vivo.

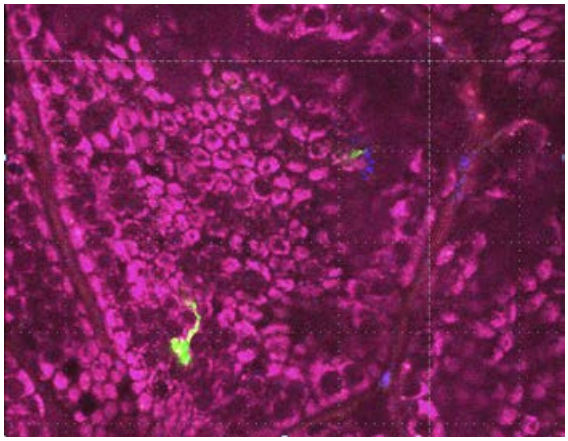
The project plan for a central Z.I.E.L building is coordinated by Professor Rudolf Manz, Professor Enno Hartmann and Professor Werner Solbach. The groundbreaking ceremony was held on July 2nd 2015 and the construction is expected to be finalized in early 2019.

Platforms IV.2

Z.I.E.L's most important technological platforms include: (i) the Imaging Platform; (ii) the "Seahorse" equipment provided by the department of Infectious Diseases and Microbiology offering cell measurement technology, and (iii) the Cell Analysis Core unit (CAnaCore) that is run by the Institute for Systemic Inflammation Research.

Imaging IV.2.1

Optical Coherence Tomography & Multiphoton Microscopy IV.2.1.1



The imaging facility has high-end microscope equipment ranging from conventional light microscopy to laser scanning and dissection facilities, multiphoton microscopy and optical coherence tomography. The facility is run by the Institute for Biomedical Optics together with the Institute for Anatomy.
www.anat.uni-luebeck.de | www.bmo.uni-luebeck.de

Image: *Uptake of ferrous nanoparticles by cells of the gut mucosa. Yellow: GFP-positive dendritic cells.*

CAnaCore: Cell Analysis Core Facility IV.2.1.2

The Cell Analysis Core Facility (CAnaCore) of the university is a central technology platform of the Z.I.E.L that was opened in January 2013. The unit is run by the Insitute for Systemic Inflammation Research. It is open to all researchers at the UzL and the UKSH, campus Lübeck. The CAnaCore provides 'state-of-the-art' equipment and protocols for cell analysis and sorting. This comprises two cells sorters (FACSAria III, BD Biosciences; MoFlo Legacy, Beckmann Coulter), an AutoMACS Pro (Miletenyi Biotec), one cell analyzer (LSR II; BD Biosciences) and the confocal microscope system FluoView 1000 (Olympus). The CanaCore is operated by Dr. Tillmann Vollbrandt, who is not only running the machines but offers training programs for flow cytometry and data analysis. In addition, the CanaCore provides buffer systems for cell sorting. The complete "terms of use" for the CAnaCore can be found on the CAnaCore website: www.isef.uni-luebeck.de/canacore.

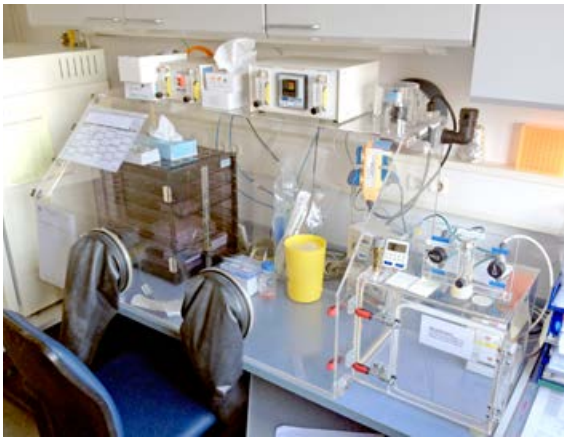
IV.2.2 Functional Analysis

IV.2.2.1 Seahorse

The Seahorse Bioanalyzer allows to monitoring mitochondrial activity and glycolytic flux of primary and immortalized cells, as well as tissue specimens. Located in a S2-facility at the Department of Infec-tious Diseases and Microbiology it is possible to establish infection models with pathogens of risk class 2, as well as genetically modified organisms. The facility is currently expanded in a way that the Seahorse analysis will be established in novel hypoxia chamber. This will allow to analyse the metabolic capacities of cells and tissues under changing environmental oxygen conditions that better reflect the physiological situation in vivo.
www.hygiene-luebeck.uk-sh.de

IV.2.2.2 Hypoxia Facility

Considering environmental factors as an integral part of physiological but also pathological mechanisms to interfere with infectious and inflammatory processes we built up a hypoxia facility at the Department of Infectious Diseases and Microbiology. Two hypoxia chambers allow complete control of the surrounding oxygen availability for characterization of host-pathogen interactions, innate and adaptive immune regulation and pathogen growth in low oxygen environment. In 2016 the novel chamber will be equipped with Bioanalyzer and an automated fluorescence microscope allowing the analyses of metabolic cell activation and host-pathogen interactions in living cells under hypoxia.
www.hygiene-luebeck.uk-sh.de



IV.2.2.3 Animal Facilities

The opening of the university's new animal facilities in 2015 has been a result of a 7 million Euro investment into highest standards for a new infrastructure.
www.gth.uni-luebeck.de

Professor Köhl's academic coordination of these new facilities is accompanied by the technical and administrative management of Dr. Barthel Schmelting.

Genetic Analysis IV.2.3

With support from the University of Lübeck and the DFG excellence cluster Inflammation at interfaces Z.I.E.L established a Genomics Animal Platform (www.lied.uni-luebeck.de) to support active groups within Z.I.E.L, UzL and the cluster. The platform is equipped with the latest technologies e.g. Illumina MiSeq machine, and has access to a good IT-Platform. It offers the following services:

- Quantitative trait locus (QTL) mapping
- Marker-assisted backcrossing (→ speed congenics; microsatellite, SNP, Illumina arrays)
- Genetic quality control (Illumina array, Affymetrix diversity array, SNP markers)
- rRNA-based Gut and skin Microbiota analysis

Biobanking and Registries IV.2.4

National Reference Center for Mycobacteria IV.2.4.1

The National Reference Center at the Resaerch Center Borstel sets golden standard for diagnosis and antibiotic susceptibility of mycobacteria. The large number of samples (12.000/year) serves as basis for epidemiologic studies for improvement of diagnostic techniques and as educational platform for numerous guests around the world. The center is also listed as Supranational Reference Laboratory by the WHO. It is a lighthouse example of cross-fertilization between basic tuberculosis research and immediate application.

www.fz-borstel.de

Registry and Biobank for Autoimmune Blistering Dermatoses IV.2.4.2

Z.I.E.L's largest project on systematic sample management takes place in the Clinic of Dermatology. Based on the routine autoimmune laboratory of the clinic and two consortia, the *German Autoimmune Bullous Disease Genetic Study Group* (21 centers; coordinator, Prof. Schmidt) and the *International Autoimmune Bullous Disease Study Group* (15 centers; coordinators: Prof. Schmidt, Prof. Ibrahim). Until 2014 1.000 DNA samples, 12.000 serum samples, and 1.000 skin biopsies of autoimmune blistering disease patients have been collected. We hope to further extend this collection and also include PBMCs and skin microbiota in cooperation with UzL Central Biobank ICB-L ensuring the highest quality of material management.

With the help of the Clinical Research Unit (KFO 303) *Pemphigoid Diseases* the first registry for autoimmune bullous diseases will be established in Europe. In the first period, the registry will be inaugurated in Schleswig-Holstein to be further expanded to a national registry in the second funding period. The registry will be operated in close cooperation with Prof. Katalinic at the Institute for Social Medicine and Epidemiology.
www.lied.uni-luebeck.de

IV.2.4.3 Sample Collection of Clinical Research Unit 170: Granulomatosis with polyangiitis

Until 2014 over 500 DNA samples of patients with ANCA-associated vasculitides have been collected through the Clinical Research Unit 170. The sample collection is continued and further extended. It also includes serum samples and peripheral leukocytes as well as samples from other rheumatic diseases, in collaboration with UzL Central Biobank ICB-L ensuring the highest quality of material management. With regard to tissue samples our group also collaborates with the Vasculitis Reference Center at the Institute of Pathology (Coordinator: Dr. Holl-Ulrich).
www.rheuma.uni-luebeck.de

Challenges and Perspective V

Infection and inflammation research will always be a major part in the biomedical sciences. Z.I.E.L will contribute to new challenges in the era of individualised medicine by being in the forefront of development of new molecular tools for improving diagnosis and establish grounds for tailored precision-therapy in the area of inflammatory skin and lung diseases and, in the future also of systemic vascular diseases. The close interactions between the immune system and the brain with ensuing metabolic components become increasingly evident. Z.I.E.L together with CBBM has outstanding opportunities and a bright future to make significant contributions.

A starting point is the recent establishment of a new master curriculum "Molecular Nutrition". Together with long-standing partners at northern universities, Z.I.E.L researchers will play important parts in shaping new initiatives like the Excellence Initiative 2.0 or the further development of the German Health Centers.

www.ziel.uni-luebeck.de

Annex: Z.I.E.L Members and Publications VI

Clinical Departments

Clinic for Anaesthesiology

Head and Chair: Prof. Dr. Carla Nau

Profile: Research at the Department of Anaesthesiology focuses on biomedical engineering and the investigation and treatment of cardiovascular diseases including approaches from immunology, endocrinology and molecular biology. In addition, there are several projects for the exploration of psychomotoric and emotional effects of narcosis, pain and intensive care, which also include ethical, legal and historical dimensions of anaesthesiological procedures.

Website: www.uksh.de/anaesthesie-luebeck

Z.I.E.L Publications:

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Sender V, Lang L, Stamme C. **Surfactant protein-A modulates LPS-Induced TLR4 localization and signaling via ß-arrestin 2**. PLoS ONE 8: e59896; 2013.

Gorrasi J, Eleftheriadis A, Takala J, Brandt S, Djafarzadeh S, Bruegger LE, Jakob SM. **Different contribution of splanchnic organs to hyperlactatemia in fecal peritonitis and cardiac tamponade**. Biomed Res Int 2013, 251084.

Clinic for Dermatology, Allergology, and Venerology

Head and Chair: Prof. Dr. Detlef Zillikens

Profile: The Clinic of Dermatology focuses on autoimmune blistering dermatoses and allergological phenomena. The clinic is a national and international reference center for autoimmune blistering diseases. Both pemphigus and bullous pemphigoid were among the top 10 diagnoses of the in-patients in 2014. In conjunction with the CCIM, patients with autoimmune blistering diseases are also seen in a busy out-patients clinic. The routine autoimmune laboratory is specialized on the diagnosis of these disorders and performs more than 30.000 analyses of sera and skin biopsies per year. In the Cluster Laboratory *Human Immunophenotyping*, high throughput analyses of blood and skin samples are offered. In 2014, the Clinic of Dermatology, CCIM, and the Lübeck Institute of Experimental Dermatology (LIED) have founded a novel core structure within the UzL, the *Center for Autoimmune Blistering Diseases Research* (CAIBR) to harbor all project on these disorder in the different institutes.

Website: www.derma.uni-luebeck.de

Institute for Experimental Dermatology (LIED)[1]

Chairs: Prof. Dr. Saleh Ibrahim, Prof. Dr. Ralf Ludwig, Prof. Dr. Dr. Enno Schmidt

Profile: LIED conducts research on genetic of autoimmune and chronic inflammatory skin diseases and on identification, validation and translation of novel therapeutics improving the diagnosis and treatment of patients suffering diseases like pemphigoid, pemphigus, lupus and psoriasis. Our mission at LIED is to identify the genetic and molecular basis of those diseases. In addition the teaching activities of the LIED contribute to courses for students of Molecular Life Science, Infection Biology and Medicine.

Website: www.lied.uni-luebeck.de

Z.I.E.L Publications:

Mersmann M, Dworschak J, Ebermann K, Komorowski L, Schlumberger W, Stöcker W, Zillikens D, Probst C, Schmidt E. **Immunoadsorber for specific apheresis of autoantibodies in the treatment of bullous pemphigoid**. Arch Dermatol Res. 2016 Jan;308(1):31-8.

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Clinic for Ear, Nose and Throat Diseases

Head and Chair: Prof. Dr. Barbara Wollenberg

Profile: Besides a broad surgical spectrum for patent care, the ENT Department conducts research on tumor biology and otitis media. The oncological approach focuses on the molecular characterization of squamous cell carcinoma and the development of innovative immunotherpeutical approaches. Otitis Media is one of the most prevalent diseases of childhood in children with more office visits and drug purchases than any other disease in the first 6 years of life. Given the high chronicity, the risks and the costs, there is an urgent need for better treatment. Recent projects on middle ear mucosa aim to identify mechanisms of "pattern recognition receptor"-TNF pathways and develop possible new targets for further therapeutic studies and new approaches to treat acute and chronic OM.

Website: www.hno.uni-luebeck.de

Z.I.E.L Publications:

Linke R, Pries R, Könnecke M, Bruchhage KL, Böscke R, Gebhard M, Wollenberg B. **The MEK1/2-ERK1/2 pathway is activated in chronic rhinosinusitis with nasal polyps**. Arch Immunol Ther Exp (Warsz). 2014 Jun;62(3):217-29.

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Linke R, Pries R, Könnecke M, Bruchhage KL, Böscke R, Gebhard M, Wollenberg B. **Increased activation and differentiated localization of native and phosphorylated STAT3 in nasal polyps**. Int Arch Allergy Immunol. 2013;162(4):290-8.

Linke R, Pries R, Könnecke M, Bruchhage KL, Böscke R, Gebhard M, Wollenberg B. **Glycogen synthase kinase 3 in chronic rhinosinusitis: two faces of a single enzyme in one disease**. Ann Allergy Asthma Immunol. 2013 Feb; 110(2):101-6.

Clinic for Internal Medicine, Unit I

Acting Director: Prof. Dr. Jürgen Steinhoff

Profile: Research at the Clinic for Internal Medicine I has a strong focus on the pathophysiology of the metabolic syndrome in the context of interactions between brain, behavior and metabolism. One of the emerging areas in research on the interaction of the microbiome with metabolism and its consequences for inflammatory precesses (metaflammation). In addition, inflammatory pathophysiology is studied with focus on the kidney and the gut.

Website: www.innere1.uni-luebeck.de

Z.I.E.L Publications:

Westermann J, Lange T, Textor J, Born J. **System consolidation during sleep – a common principle underlying psychological and immunological memory formation**. Trends Neurosci. 2015 Oct;38(10):585-97.

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Department of Internal Medicine, Unit III

Head and Chair: Prof. Dr. Peter Zabel

Profile: Researchers at Unit III of the Clinic for Internal Medicine investigate pathogen-induced inflammation in the pulmonary compartment. The main focus is persistent infections with intracellular pathogens such as *C. pneumonia* and *H. influenzae*. The methods used include a human lung tissue infection model which enables the study of the in vitro host response to pathogen challenge in patients with different underlying pulmonary diseases as COPD and interstitial lung diseases. The clinical focus lies on the medical and interventional treatment of chronic obstructive lung diseases, lung cancer, acute lung injury and lung infections including an intermediate/intensive care unit with possibility of noninvasive ventilation.

Website: www.innere3.uni-luebeck.de

Z.I.E.L Publications:

Honselmann KC, Buthut F, Heuwer B, Karadag S, Sayk F, Kurowski V, Thiele H, Droemann D, Wolfrum S. **Long-term mortality and quality of life in intensive care patients treated for pneumonia and/or sepsis: Predictors of mortality and quality of life in patients with sepsis/pneumonia**. J Crit Care 2015 Aug;30(4):721-6. Epub 2015 Mar 13.

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Association of German Allergologists (AeDA) and the Society for Pediatric Allergology and Environmental Medicine (GPA). Allergo J Int. 2014;23(1):1-16. Review.

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Clinic for Neurology

Head and Chair: Prof. Dr. Thomas Münte

Profile: Scientific activities at the Department of Neurology take place within seven research groups: Cognitive Electrophysiology, Cognitive Nerology, Social and Affective Neurosciences, Sensomotorics, Neurobiochemistry and Neurovascular Research.

Website: www.neuro.uni-luebeck.de

Z.I.E.L Publications:

Malter MP, Frisch C, Schoene-Bake JC, Helmstaedter C, Wandinger KP, Stoecker W, Urbach H, Surges R, Elger CE, Vincent AV, Bien CG. **Outcome of limbic encephalitis with VGKC-complex antibodies: relation to antigenic specificity**. J Neurol. 2014 Sep;261(9):1695-705.

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Leypoldt F, Gelderblom M, Schöttle D, Hoffmann S, Wandinger KP. **Recovery from severe frontotemporal dysfunction at 3 years after N-methyl-d-aspartic acid (NMDA) receptor antibody encephalitis**. J Clin Neurosci. 2013 Apr;20(4):611-3.

Jarius S, Martínez-García P, Hernandez AL, Brase JC, Borowski K, Regula JU, Meinck HM, Stöcker W, Wildemann B, Wandinger KP. **Two new cases of anti-Ca (anti-ARHGAP26/GRAF) autoantibody-associated cerebellar ataxia**. J Neuroinflammation. 2013 Jan 15;10:7.

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Clinic for Ophthalmology

Head and Chair: Prof. Dr. Salvatore Grisanti

Profile: Scientific activities at the Department of Ophthalmology take place in the following research areas: Pathomechanisms of AMD; Vitreoretinale Interface; Medication-based treatment of wound-healing; Malignant Uveal Melanoma; Neovascular Diseases; Pigment Cell Research; Inhibition of Proliferative Vitreoretinopathy.

Website: www.ophtha.uni-luebeck.de

Z.I.E.L Publications:

Grisanti S, Zhu Q, Tatar O, Lüke J, Lüke M, Tura A, Grisanti S. **(2015) Differential expression of vascular endothelial growth factor – a isoforms in neovascular age-related macular degeneration**. Retina 35: 764-72.

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Schuler-Thurner B, Bartz-Schmidt KU, Bornfeld N, Cursiefen C, Fuisting B, Grisanti S, Heindl LM, Holbach L, Keserü M, Knorr H, Koch K et al. **(2015) Immunotherapy of uveal melanoma: vaccination against cancer: Multicenter adjuvant phase 3 vaccination study using dendritic cells laden with tumor RNA for large newly diagnosed uveal melanoma**. Ophthalmologe 112: 1017-21.

Januschowski K, Schnichels S, Hagemann U, Koch V, Hofmann J, Spitzer MS, Bartz-Schmidt KU, Szurman P, Lüke M, Aisenbrey S. **(2014) Electrophysiological toxicity testing of VEGF Trag-Eye in an isolated perfused vertebrate retina organ culture model**. Acta Ophthalmol 92: e305-11.

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Ranjbar M, Gross N, Evers C, Hua J, Martin G, Schulze B, Michaelis U, Hansen L, Agostini HT. **(2013) Reduced choroidal neovascularization by targeted drug delivery with Endo TAG-1 or targeted PDT with verteporfin encapsulated in cationic liposomes**. Molecular Vision 19: 54-61.

Ranjbar M, Grisanti S. **(2013) Stammzelltherapie zum Ersatz des RPE**. Ophthalmologische Nachrichten 08: 14.

Ranjbar M, Grisanti S, Brüggemann A. **(2013) Vernarbendes Schleimhautpemphigoid: Klinische Varianz der okulären Manifestation**. Der Augenspiegel 10: 32.

Clinic for Pediatrics Diseases

Head and Chair: Prof. Dr. Egbert Herting

Profile: Research at the Department of Pediatrics is divided into six major areas: Diabetology and Endocrinology (Hormone Center); Neonatology and Innate Immunity; Immunology and Infectious Diseases; Neuropediatrics and Social Pediatrics; Perinatal Medicine and Pediatric Intensive Care; Pneumology and Allergology; Clinical Trials.

Website: www.uksh.de/paediatrie-luebeck

Z.I.E.L Publications:

Rose K, Kopp MV. **Pediatric investigation plans for specific immunotherapy: Questionable contributions to childhood health**. Pediatr Allergy Immunol. 2015 Dec; 26(8):695-701.

Buchheidt D, Spiess B, Cornely OA, Vehreschild M, Groß U, Bader O, Hamprecht A, Lauten M, Rath P-M, Steinmann J, Hofmann W-K. **Azol-Resistenz bei Aspergillus fumigatus – Epidemiologie und Nachweis bei immunsupprimierten Patienten in Deutschland**. Dtsch Med Wochenschr. 2014 Jun;139(25-26):1373-1376

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Puzik A, Thiel A, Faust K, Härtel C. **Thalidomide has anti-inflammatory properties in neonatal immune cells**. Innate Immun. 2013 Feb;19(1):42-52.

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Härtel C, Scholz T, Kuhn M, Bendiks M, Göpel W, Lauten M, Herting E. **Innate immune responses to Stenotrophomonas maltophilia in immunocompromised pediatric patients and the effect of taurolidine**. J Microbiol Immunol Infect. 2013 Apr;46(2):115-20.

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Department of Plastic Surgery

Head and Chair: Prof. Dr. Peter Mailänder

Profile: The clinic has a long-standing expertise in research on angiogenesis in ischemic tissue and has excellent facilities to monitor biochemical and microcirculatory changes in free micro-vascular flaps. In addition, understanding the pathophysiology of infections of the hands is one of the research missions of the Clinic.

Website: www.plastische-chirurgie-luebeck.uk-sh.de

Z.I.E.L Publications:

Bode-Böger SM, Schopp B, Tröger U, Martens-Lobenhoffer J, Kalousis K, Mailänder P. **Intravenous colistin in a patient with serious burns and borderline syndrome: the benefits of therapeutic drug monitoring**. Int J Antimicrob Agents 42(4):357-60, 2013.

Department of Rheumatology – Clinic for Rheumatology

Head and Chair: Prof. Dr. Gabriele Riemekasten

Profile: The research focus in the Clinic for Rheumatology are systemic small vessel vasculitides. Researchers have mad significant contribution to clinical entities like granulomatosis with polyangiitis (M. Wegener) or eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome). The Clinic heads or contributes to numerous clinical or pre-clinical studies related to ANCA-associated Vaskulitides, Sklerodermie, systemic Lupus erythematodes, Rheumatoid Arthritis, Spondylarthropathies. The Clinic is founding member of the European working group on vasculitides EUVAS, and acting member in OMERACT (Outcome Measure in Rheumatology) and VRC (Vasculitis Research Consortium).

Website: www.rheuma.uni-luebeck.de

Z.I.E.L Publications:

Humrich JX, von Spee C, Riemekasten G. **Stärkung der regulatorischen T-Zellen durch Interleukin-2 Therapie**. Drug Res (Stuttg). 2015 Nov; 65 Suppl 1:S23. Epub 2015 Nov 4. German. No abstract available.

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Hunzelmann N, Riemekasten G, Becker M, Moinzadeh P, Kreuter A, Melchers I, Mueller-Ladner U, Meier F, Worm M, Lee H, Herrgott I, Pfeiffer C, Fierlbeck G, Henes J, Juche A, Zeidler G, Mensing H, Günther C, Sárdy M, Burkhardt H, Koehm M, Kuhr K, Krieg T, Sunderkötter C. **The Predict Study: Low risk for digital ulcer development in Systemic Sclerosis patients with increasing disease duration and lack of topoisomerase-1 antibodies**. Br J Dermatol. 2015 Dec 26. [Epub ahead of print] PMID: 26708835.

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López-Isac E, Campillo-Davo D, Bossini-Castillo L, Guerra SG, Assassi S, Simeón CP, Carreira P, Ortego-Centeno N, García de la Peña P; Spanish Scleroderma Group, Beretta L, Santaniello A, Bellocchi C, Lunardi C, Moroncini G, Gabrielli A, Riemekasten G, Witte T, Hunzelmann N, Kreuter A, Distler JH, Voskuyl AE, de Vries-Bouwstra J, Herrick A, Worthington J, Denton CP, Fonseca C, Radstake TR, Mayes MD, Martín J. **Influence of TYK2 in systemic sclerosis susceptibility: a new locus in the IL-12 pathway**. Ann Rheum Dis. 2015 Sep 2. pii: annrheumdis-2015-208154. [Epub ahead of print]

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Moosig F, Bremer JP, Hellmich B, Holle JU, Holl-Ulrich K, Laudien M, Matthis C, Metzler C, Nölle B, Richardt G, Gross WL. **A vasculitis centre based management strategy leads to improved outcome in eosinophilic granulomatosis and polyangiitis (Churg-Strauss, EGPA): monocentric experiences in 150 patients**. Ann Rheum Dis. 2013 Jun; 72(6):1011-7. Epub 2012 Aug 11.

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Clinic for Surgery

Head and Chair: Prof. Dr. Tobias Keck

Profile: The main mission of the Clinic is the understanding of molecular changes in colorectal cancer and to develop new biomarkers for early diagnosis, treatment and prevention. In addition, understanding metastatic processes are in the focus of research. In the context of inflammation medicine, parallels between tumorigenic and inflammatory processes are uncovered.

Website: www.chirurgie.uni-luebeck.de

Z.I.E.L Publications:

Rotta Detto Loria J, Rohmann K, Droemann D, Kujath P, Rupp J, Goldmann T, Dalhoff K. **Nontypeable Haemophilus Influenzae Infection Upregulates the NLRP3 Inflammasome and Leads to Caspase-1-Dependent Secretion of Interleukin-1β – A Possible Pathway of Exacerbations in COPD**. PLoS One. 2013 Jun 26;8(6):e66818.

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Pre-Clinical Departments

Institute for Anatomy

Head and Chair: Prof. Dr. Jürgen Westermann

Profile: Research is focused on the mechanisms regulating mucus transport and immune responses in the lung under normal and pathological conditions. In addition, T-cell migration and T-cell repertoire are analyzed and the consequences regarding T-cell memory are studied. Advanced imaging techniques (e.g. laser-microdissection, two-photon microscopy, electron microscopy) and next-generation sequencing are used in order to obtain in depth information of the local microenvironment in vivo. Anatomy teaching is conducted in all study courses of the university and aspects of lung biology and T-cell immunology are presented in the framework of the graduate program in Molecular Life Science and Infection Biology.

Website: www.anat.uni-luebeck.de

Z.I.E.L Publications:

Ansari R, Buj C, Pieper M, König P, Schweikard A, Hüttmann G. **Microanatomical and functional assessment of ciliated epithelium in mouse trachea using optical coherence phase microscopy**. Opt Express. 2015 Sep 7;23(18):23217-24.

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Institute for Biochemistry

Head and Chair: Prof. Dr. Dr.h.c. Rolf Hilgenfeld

Profile: The Institute uncovers (i.) the molecular basis of intracellular Infections (SARS, HIV, *Legionella pneumophila, Streptococcus dysgalactiae subsp. equisimilis*). (ii.) the structural genomics, biochemistry and function of human coronaviruses, Lassavirus and Sappovirus with the aim to deliver targets for new antivirals and (iii.) structural and functional proteomics of bacterial pathogens like salmonella, legionella and chlamydia.

Website: www.biochem.uni-luebeck.de

Z.I.E.L Publications:

Kohlmann F, Shima K, Rupp J, Solbach W, Hilgenfeld R, Hansen G. **Production, crystallization and X-ray diffraction analysis of the protease CT441 from Chlamydia trachomatis**. Acta Crystallogr F Struct Biol Commun. 2015 Dec 1;71(Pt 12):1454-8.

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Comprehensive Center for Inflammation Medicine (CCIM)

Head and Chair: Prof. Dr. Diamant Thaçi

Profile: The Comprehensive Center for Inflammation Medicine is an outpatient clinic for inflammation diseases at the University Hospital Schleswig-Holstein, which allows the best possible patient care through collaboration between different specialists and a comprehensive approach of the Inflammation Research Excellence Cluster. The facilities are one of a kind in Germany: patients with multiple, sometimes non-specific inflammatory diseases find all specialists at one place in the CCIM, from internists, gastroenterologists, dermatologists, pulmonologists and cardiologists to neurologists, rheumatologists or dentists. Research at Lübeck`s CCIM conducts a wide range of clinical trials and offers clinical research support for cohort studies within the DFG funded Center of Excellence "Inflammation at Interfaces".

Website: www.entzuendungsmedizin.uk-sh.de

Z.I.E.L Publications:

Blome C, Gosau R, Radtke MA, Reich K, Rustenbach SJ, Spehr C, Thaçi D, Augustin M. **Patient-relevant treatment goals in psoriasis**. Arch Dermatol Res. 2016 Mar;308(2):69-78. Epub 2015 Dec 19.

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Thaçi D, Augustin M, Krutmann J, Luger T. **Importance of basic therapy in psoriasis**. J Dtsch Dermatol Ges. 2015 May;13(5):415-8.

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Institute for Medical Microbiology and Hygiene (until Sept. 30th 2015)

Head and Chair: Prof. Dr. Werner Solbach

The institute was closed in Sept. 2015 and part of it has been constitutive for the newly created Department of Infectious Diseases and Microbiology.

Department of Infectious Diseases and Microbiology (since October 2015)

Head and Chair: Prof. Dr. Jan Rupp

The Department of Infectious Diseases and Microbiology (KIM) was founded in October 2015 as a merger between the former Institute for Medical Microbiology and Hygiene (Prof. Dr. W. Solbach) and the Section for Infectious Diseases in the Medical Clinic III (Prof. Dr. P. Zabel).

Profile: Research in the Institute focusses (i.) on the understanding of the pathogenesis and innate immune mechanisms after mammalian infection with intracellular non-viral organisms like Leishmania, Anaplasma, Chlamydia, Histoplasma; (ii.) genetics of antibiotic resistance and biofilm formation in staphylococci; (iii.) molecular epidemiology of disease outbreaks.Within the Department specialists for diagnostic microbiology and infectious diseases are working together to cover all aspects in diagnosing and treating patients suffering from an infectious process. The current research focus addresses experimental and clinical questions, with regard to host-pathogen interactions but also infection epidemiology. Special attention of the experimental work is given to infections with intracellular pathogens, the role of neutrophils in inflammation and infection, and the immune-modulatory capacity of oxygen. In addition, identifying novel microbial patterns in all kinds of inflammatory and infectious diseases represent a valuable intersection between current research activities and future diagnostic perspectives.

Website: www.uksh.de/Infektiologie_Mikrobiologie

Z.I.E.L Publications:

Knobloch J, Chikosi SJ, Yanik S, Rupp J, Jungck D, Koch A. **A systemic defect in Toll-like receptor 4 signaling increases lipopolysaccharide-induced suppression of IL-2-dependent T-cell proliferation in COPD**. Am J Physiol Lung Cell Mol Physiol. 2016 Jan 1;310(1):L24-39. Epub 2015 Oct 23.

Wagner C, Goldmann T, Rohmann K, Rupp J, Marwitz S, Rotta Detto Loria J, Limmer S, Zabel P, Dalhoff K, Drömann D. **Budesonide Inhibits Intracellular Infection with Non-Typeable Haemophilus influenzae Despite Its Anti-Inflammatory Effects in Respiratory Cells and Human Lung Tissue: A Role for p38 MAP Kinase**. Respiration. 2015;90(5):416-25. Epub 2015 Oct 10.

Krämer S, Crauwels P, Bohn R, Radzimski C, Szaszák M, Klinger M, Rupp J, van Zandbergen G. **AP-1 Transcription Factor Serves as a Molecular Switch between Chlamydia pneumoniae Replication and Persistence**. Infect Immun. 2015 Jul;83(7):2651-60. Epub 2015 Apr 20.

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Institute for Molecular Medicine

Head and Chair: Prof. Dr. Georg Sczakiel

Profile: The Institute´s interest is in the understanding of the uptake of naked nucleic acids by mammalian cells. In translational medicine, the biochemistry, molecular biology and pre-clinical application of nucleic acid-based drugs and the development of non-invasive diagnostic approaches based on extracellular nucleic acids in body fluids is in the focus.

Website: www.molmed.uni-luebeck.de/laboratories.html

Z.I.E.L Publications:

Petkovic S, Badelt S, Block S, Flamm C, Delcea M, Hofacker I, Müller S. **Sequence-controlled RNA self-processing: computational design, biochemical analysis, and visualization by AFM**. RNA. 2015 May 21. [Epub ahead of print].

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Institute for Experimental and Toxicological Pharmacology

Head and Chair: Prof. Dr. Markus Schwaninger

Profile: Research of the Institute focuses on pharmacology at the interface of brain and periphery, mainly the immune system. On the one side our work touches actions of the immune system in the CNS, e.g., in multiple sclerosis or stroke. On the other side we investigate immunological consequences of neural activity, e.g., fever. Center stage is taken by the blood-brain barrier, the interface between brain and periphery that is involved in this cross-talk.

Website: www.pharma.uni-luebeck.de

Z.I.E.L Publications:

Gliem M, Schwaninger M, Jander S. **Protective features of peripheral monocytes/macrophages in stroke**. Biochim Biophys Acta, 2015 Nov 12. Epub ahead of print]

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Assmann JC, Körbelin J, Schwaninger M. **Genetic manipulation of brain endothelial cells in vivo**. Biochim Biophys Acta, 2015 Oct 8. [Epub ahead of print].

Lopes Pinheiro MA, Kooij G, Mizee MR, Kamermans A, Enzmann G, Lyck R, Schwaninger M, Engelhardt B, de Vries HE. **Immune cell trafficking across the barriers of the central nervous system in multiple sclerosis and stroke**. Biochim Biophys Acta, 2015 Oct 22. [Epub ahead of print].

Qadri F, Rimmele F, Mallis L, Häuser W, Dendorfer A, Jöhren O, Dominiak P, Leeb-Lundberg LM, Bader M. **Acute hypothalamo-pituitary-adrenal axis response to LPS-induced endotoxemia: expression pattern of kinin type B1 and B2 receptors**. Biol Chem, 2015 Oct 15.

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Institute for Systemic Inflammation Research

Head and Chair: Prof. Dr. Jörg Köhl

Profile: One research focus at ISEF is on the complement system and its role in the regulation of infectious and non-infectious inflammatory diseases including allergic and autoimmune diseases. More specifically, we are interested in the role of the different cleavage fragments of C3 and C5 in the regulatory network of innate and adaptive immunity. A particular emphasis is on the cross-talk with pattern-recognition receptors, IgG Fc receptos and the regulation of B and- T cell responses. A second research foucs is on the differentiation, homing and interaction of B cells and plasma cells with their special micro-compartments (niches) in lymphoid and inflamed tissues and their roles for the development of allergic diseases, autoimmunity and B cell neoplasia.

Website: www.isef.uni-luebeck.de

Z.I.E.L Publications:

Karsten CM, Laumonnier Y, Eurich B, Ender F, Bröker K, Roy S, Czabanska A, Vollbrandt T, Figge J, Köhl J. **Monitoring and Cell-Specific Deletion of C5aR1 Using a Novel Floxed GFP-C5aR1 Reporter Knock-in Mouse**. J Immunol. 2015 Feb 15;194(4):1841-55.

Strait RT, Posgai MT, Mahler A, Barasa N, Jacob CO, Köhl J, Ehlers M, Stringer K, Shanmukhappa SK, Witte D, Hossain MM, Khodoun M, Herr AB, Finkelman FD. **IgG1 protects against renal disease in a mouse model of cryoglobulinaemia**. Nature. 2015 Jan 22;517(7535):501-4.

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Schulze FS, Beckmann T, Nimmerjahn F, Ishiko A, Collin M, Köhl J, Goletz S, Zillikens D, Ludwig R, Schmidt E. **Fc γRIIB, Fc γRIII and Fc γRIV mediate tissue destruction in experimental bullous pemphigoid**. 2014 Am. J. Pathol. 184:2185-2196.

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Chen H, Assmann JC, Krenz A, Rahman M, Grimm M, Karsten CM, Köhl J, Offermanns S, Wettschurek N, Schwaninger M. **HCA2 mediates the protective effect of dimethyl fumarate in experimental autoimmune encephalomyelitis**. 2014 J. Clin. Invest. 124:2188-2192.

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Z.I.E.L Publications:

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Z.I.E.L Partners

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Z.I.E.L Publications:

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