Leibniz Institute for Natural Product Research and Infection Biology
Hans Knöll Institute

RESEARCH REPORT

2016 | 2017

Leibniz Association

RESEARCH REPORT 2016 | 2017

VORWORT

Der Geist des Fortschritts der vergangenen Jahre lebte auch 2016 und 2017 weiter: Das Leibniz-Institut für Naturstoff-Forschung und Infektionsbiologie – Hans-Knöll-Institut (Leibniz-HKI) kann auf zwei erfolgreiche und wissenschaftlich bereichernde Jahre zurückblicken.

Mit Hans Peter Saluz und Reinhard Guthke verabschiedeten wir zwei renommierte Wissenschaftler und geschätzte Kollegen aus dem aktiven Berufsleben. Beide haben das Leibniz-HKI über Jahrzehnte hinweg geprägt und wir freuen uns, dass sie dem Institut auch weiterhin verbunden bleiben. Zugleich begrüßten wir Gianni Panagiotou als neuen Leiter der Forschungsgruppe Systembiologie und Bioinformatik. Zuvor war er Associate Professor und Leiter der Gruppe Biologie und Bioinformatik an der Universität von Hongkong. Sein Weg dorthin hatte ihn über das Studium und die Promotion an der Nationalen Technischen Universität von Athen und die Technische Universität Dänemark, wo er als Postdoc arbeitete, geführt.

Oliver Kurzai nahm den Ruf auf den Lehrstuhl für Mikrobiologie und Mykologie am Universitätsklinikum Würzburg an. Er leitet weiterhin die Forschungsgruppe Fungal Septomics am Zentrum für Innovationskompetenz Septomics und das Nationale Referenzzentrum für Invasive Pilzinfektionen am Leibniz-HKI. Mit der Berufung von Oliver Kurzai nach Würzburg hat das Leibniz-HKI erstmals eine personelle Brücke zu einer universitären Einrichtung außerhalb Jenas geschlagen.

Eine neue, an das Institut assoziierte Nachwuchsgruppe Synthetische Mikrobiologie erweitert das Forschungsprofil des Leibniz-HKI und stärkt die Verbindung zur Friedrich-Schiller-Universität Jena. Für die Leitung der durch die Carl-Zeiss-Stiftung geförderten Gruppe konnten wir Gerald Lackner gewinnen, der zuvor einen Postdoc-Aufenthalt an der ETH Zürich absolviert hatte.

Auch das Biotechnikum erhielt eine neue Spitze. Miriam Agler-Rosenbaum wurde in einem gemeinsamen Verfahren mit der FSU Jena auf die Professur Synthetische Biotechnologie berufen. Sie war unter anderem Postdoc am Department of Biological and Environmental Engineering an der Cornell University Ithaca, USA, bevor sie auf die Juniorprofessur Mikrobiologie für definierte Mischkulturen an die RWTH Aachen berufen wurde. Mit der Übernahme durch Miriam Agler-Rosenbaum erhielt das Biotechnikum den Status einer Forschungsabteilung.

Erfreulich ist auch die Publikationstätigkeit der Wissenschaftlerinnen und Wissenschaftler des Leibniz-HKI. Sie veröffentlichten ihre Forschungsergebnisse in zahlreichen anerkannten Fachjournalen wie Nature, *Nature Chemical Biology, Nature Communications, Nature Scientific Reports, Angewandte Chemie International Edition, Nucleic Acids Research* und *PNAS*.

Doch nicht nur Veröffentlichungen in namhaften Zeitschriften zeigen die hohe Qualität der Forschung am Leibniz-HKI. So richtete das Institut wichtige Kongresse aus, darunter die Jahrestagung 2016 der Vereinigung für Allgemeine und Angewandte Mikrobiologie, die Thüringer EFRE-Jahrestagung 2016 oder die Life meets Light – First Scientific Conference of the Leibniz ScienceCampus InfectoOptics 2017.

Im Berichtszeitraum gelang es zudem, das Drittmittelaufkommen weiter zu steigern. Das schlägt sich nicht zuletzt im Wachstum der Beschäftigtenzahlen, den erreichten akademischen Abschlüssen und der Qualität der veröffentlichten Originalarbeiten nieder. Inzwischen übersteigt die Summe der Drittmittel die Hälfte der Grundfinanzierung des Instituts, wobei wir unsere Drittmittelaktivitäten streng an die Entwicklung des strategischen Forschungsprofils und die Qualität der Forschung koppeln. Besonderes Augenmerk gilt daher unserer Beteiligung an streng evaluierten Sonderforschungsbereichen. Mit Bewilligung der zweiten Förderphase des SFB/Transregio 124 FungiNet und der Neueinrichtung des SFB 1278 PolyTarget ist das Leibniz-HKI nunmehr an vier Sonderforschungsbereichen beteiligt – neben FungiNet und PolyTarget auch am SFB 1127 ChemBioSys und am SFB 1192 Immune-Mediated Glomerular Diseases.

Erneut konnten Forscherinnen und Forscher des Leibniz-HKI in den zurückliegenden beiden Jahren zahlreiche Preise und Auszeichnungen für ihre Arbeiten gewinnen. Sie würdigen die erreichten Ergebnisse und motivieren für den Labortalltag. So konnte das Team um Christian Hertweck für den neu entdeckten antibiotischen Wirkstoff Clostrubin erneut den Titel Leibniz-Wirkstoff des Jahres an das Leibniz-HKI holen. Besonders hoch schätzen wir das langjährige Engagement der medac GmbH, die mit ihrem Geschäftsführer Nikolaus Graf zu Stolberg im Kuratorium des Leibniz-HKI vertreten ist. Der medac Forschungspreis würdigt herausragende Originalpublikationen zu den Forschungsschwerpunkten des Leibniz-HKI, die in Kooperation mehrerer Gruppen des Instituts entstanden. Damit spornt der attraktiv dotierte Preis vor allem den wissenschaftlichen Nachwuchs zur Zusammenarbeit und zum Ideenaustausch an.

Infolge der zahlreichen drittmittelfinanzierten Verbundprojekte ist die Mitarbeiterzahl des Leibniz-HKI weiter angestiegen. Von den rund 430 Mitarbeitern sind 140 Doktoranden. Der Aufwuchs der vorangegangenen Jahre hat nun auch bauliche Folgen: zwei alte Laborgebäude sollen durch das deutlich größere HKI Biotech Center ersetzt werden. Möglich wurde der Neubau durch die Empfehlung der Bewertungskommission im Zuge der außerordentlich positiven Bewertung und Entwicklungsprognose bei der Evaluierung des Instituts im Jahr 2014.

Um die gesellschaftliche Bedeutung von Infektionskrankheiten zu betonen, unterzeichnete das Leibniz-HKI gemeinsam mit anderen namhaften Akteuren einen Aufruf an die Bundesregierung. Mit dem Memorandum „Kampf gegen Infektionskrankheiten verstärken und Leben retten!“ warnten die Unterzeichner vor den Gefahren einer post-antibiotischen Ära und machten den dringenden Handlungsbedarf deutlich.

Ein besonderer Höhepunkt war der Besuch des Bundespräsidenten Joachim Gauck in Begleitung des Thüringer Ministerpräsidenten Bodo Ramelow, und des Thüringer Ministers für Wirtschaft, Wissenschaft und Digitale Gesellschaft, Wolfgang Tiefensee, am 23. November 2016. Gauck informierte sich im Rahmen einer Podiumsdiskussion mit Promovierenden und jungen Gruppenleitern über die beruflichen Chancen und Entwicklungsperspektiven in der Forschung und über die integrative Funktion der Wissenschaft in einer globalisierten Welt. Bei einem anschließenden Rundgang durch das Biotechnikum stellten wir dem interessierten Bundespräsidenten neue Forschungsansätze für die Suche nach dringend benötigten Antibiotika vor.

Axel Brakhage, Direktor HKI

INTRODUCTION

The spirit of progress of the past years continued in 2016 and 2017: The Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute (Leibniz-HKI) can look back on two successful and scientifically enriching years.

We bid farewell to Hans Peter Saluz and Reinhard Guthke, two renowned scientists and valued colleagues, who retired from active professional life. Both have shaped the Leibniz-HKI for decades and we are pleased that they will continue to be associated with the institute. At the same time we welcomed Gianni Panagiotou as the new head of the research group Systems Biology and Bioinformatics. He previously was Associate Professor and head of the Biology and Bioinformatics Group at the University of Hong Kong. Earlier stations in his career include his studies and doctorate at the National Technical University of Athens and the Technical University of Denmark, where he worked as a postdoc.

Oliver Kurzai accepted the appointment to the Chair of Microbiology and Mycology at the University Hospital of Würzburg. He continues to head the research group Fungal Septomics at the Centre for Innovation Competence Septomics and the National Reference Center for Invasive Fungal Infections at the Leibniz-HKI. With the appointment of Oliver Kurzai to Würzburg, the Leibniz-HKI has for the first time built a personnel bridge to a university institution outside Jena.

The new junior research group Synthetic Microbiology associated with the institute expands the research profile of the Leibniz-HKI and strengthens the connection to the Friedrich Schiller University Jena. Gerald Lackner, who had previously completed a postdoctoral stay at ETH Zurich, was recruited to lead the group, which is funded by the Carl Zeiss Foundation.

The Bio Pilot Plant also has a new head. Miriam Agler-Rosenbaum was appointed to the Chair of Synthetic Biotechnology in a joint procedure with the FSU Jena. She previously was a postdoc in the Department of Biological and Environmental Engineering at Cornell University Ithaca, USA, before being appointed to the junior professorship of Microbiology for Defined Mixed Cultures at the RWTH Aachen. With the appointment of Miriam Agler-Rosenbaum, the Bio Pilot Plant was given the status of a research department.

The publication activity of the scientists at Leibniz-HKI is also impressive. They published their research results in numerous renowned scientific journals such as *Nature, Nature Chemical Biology, Nature Communications, Nature Scientific Reports, Angewandte Chemie International Edition, Nucleic Acids Research* and *PNAS*.

But it is not only publications in renowned journals that show the high quality of research at Leibniz-HKI. The institute has organized important meetings, including the Annual Conference 2016 of the Association for General and Applied Microbiology, the Thuringian EFRE Annual Conference 2016 or the Life meets Light - First Scientific Conference of the Leibniz ScienceCampus InfectoOptics 2017.

In the reporting period, the volume of third party funding has also successfully been increased. This is reflected in the growing number of employees, the academic degrees achieved and the quality of the original papers published. Currently, the total of the third-party funding exceeds half of the institute's basic funding, whereby we strictly align our third-party funding activities with the development of the strategic research profile and the quality of the research. Particular attention is therefore paid to our participation in competitively evaluated Collaborative Research Centres. With the approval of

the second funding period of the CRC/Transregio 124 FungiNet and the new establishment of the CRC 1278 PolyTarget, Leibniz-HKI is now involved in four Collaborative Research Centres – in addition to FungiNet and PolyTarget, also in CRC 1127 ChemBioSys and CRC 1192 Immune-Mediated Glomerular Diseases.

Once again, researchers at the Leibniz-HKI have won numerous prizes and awards for their work over the past two years. These acknowledge the results achieved and provide motivation for the daily laboratory work. For example, Christian Hertweck's team was again awarded the title of Leibniz Drug of the Year for the newly discovered antibiotic compound clostrubin. We particularly appreciate the long-standing commitment of medac GmbH, which is represented on the Board of Trustees of the Leibniz-HKI by its managing director Nikolaus Graf zu Stolberg. The medac Research Award honours outstanding original publications on the research foci of the Leibniz-HKI, which resulted from cooperations between several groups of the institute. Thus, the attractively endowed prize particularly encourages young researchers to collaborate and exchange ideas.

Thanks to the numerous third-party funded collaborative projects, the number of employees at the Leibniz-HKI has continued to rise. Of the approximately 430 employees, 140 are doctoral researchers. The growth of the previous years has now also lead to structural consequences: Two old laboratory buildings are to be replaced by the considerably larger HKI Biotech Center. The new building was made possible by the recommendation of the evaluation commission which gave an exceptionally positive assessment and development forecast during the evaluation of the institute in 2014.

In order to emphasize the societal importance of infectious diseases, the Leibniz-HKI, together with other renowned actors, signed an appeal to the German government. With the memorandum "Strengthening the fight against infectious diseases and saving lives", the signatories warned of the dangers of a post-antibiotic era and made clear the urgent need for action.

A special highlight was the visit of the Federal President of Germany, Joachim Gauck, accompanied by the Thuringian Minister President Bodo Ramelow, and the Thuringian Minister of Economics, Science and Digital Society, Wolfgang Tiefensee, on November 23, 2016. At this occasion, Gauck talked about career opportunities and development prospects in research and the integrative function of science in a globalized world in a panel discussion with doctoral researchers and young group leaders. During a subsequent tour of the Bio Pilot Plant, we presented new research approaches for the search for urgently needed antibiotics to the interested Federal President.

Axel Brakhage, Director HKI

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DEPARTMENT

BIOMOLECULAR CHEMISTRY

DEPARTMENT **BIOMOLECULAR CHEMISTRY**

MOST IMPORTANT RESULTS

The Department Biomolecular Chemistry has investigated a variety of microorganisms as an unparalleled source of therapeutics. Since genome analyses have revealed that their full biosynthetic potential is much larger than expected, the department employs diverse strategies to unearth cryptic natural products such as genome mining, pathway engineering and triggering, as well as co-cultivation approaches. Yet, it is often essential to consider the ecological context of microbes to activate pathways and to discover biologically active compounds and their functions. These scenarios include predator-prey and pathogenic interactions, the protection of insect assets such as offspring and cultivars, as well as host protection in symbiotic relationships with plants, invertebrates and animals/humans.

In collaboration with the Kaltenpoth laboratory (University of Mainz), we have reported a successful case of ecology-driven discovery of novel antimicrobial agents. Experimental evidence supports a dynamic transition from plant pathogenicity to insect-defensive mutualism in symbiotic *Burkholderia gladioli* bacteria. In a group of herbivorous beetles, these symbionts protect the vulnerable egg stage against detrimental microbes, in particular pathogenic fungi. The production of a blend of antibiotics by *B. gladioli*, including toxoflavin, caryoynencin and two new antimicrobial compounds, the macrolide lagriene and the isothiocyanate sinapigladioside, likely mediate this defensive role. In addition to vertical transmission, these insect symbionts can be exchanged via the host plant and retain the ability to initiate systemic plant infection at the expense of the plant's fitness. Our findings provide a paradigm for the transition between pathogenic and mutualistic lifestyles and shed light on the evolution and chemical ecology of this defensive mutualism. In addition, a new antibiotic and a new antifungal agent were described.

In another collaboration (Mittag/Sasso laboratories, FSU Jena), we employed MALDI imaging to unveil a new role of lipopeptides in bacteria-microalga interactions. These biotic interactions

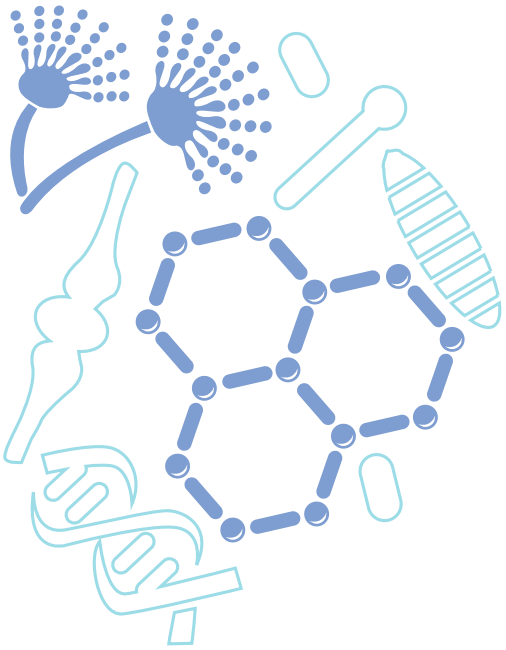

Figure 1: Expression of antibiotic encoding genes from a mangrove endophyte in *E. coli* leads to formation of indigo.

are significant because these photosynthetic unicellular organisms are key contributors to carbon fixation on Earth, and their global photosynthetic capacities may be affected by microbial communities. Yet, information on molecular factors that govern these interactions is scarce. Through imaging and analytics, we found that the bacterium *Pseudomonas protegens* strongly inhibits the growth and alters the morphology of the biflagellated green alga *Chlamydomonas reinhardtii* by means of orfamides. Orfamide A triggers an increase in cytosolic Ca^{2+} in *C. reinhardtii* and causes deflagellation of algal cells. These effects of orfamide A, which are specific to the algal class of Chlorophyceae and appear to target a Ca^{2+} channel in the plasma membrane, represent a novel biological activity for cyclic lipopeptides.

MALDI imaging was also instrumental in elucidating the induced defense of mushroom. In collaboration with the Hoffmeister laboratory (FSU Jena), the secretion of antilarval mushroom polyenes (18-methyl-19-oxoicosaoctaenoic acid and 20-methyl-21-oxodocosanonaenoic acid) was visualized in response to injury of the mycelium of the stereaceous mushroom BY1. Interestingly, the polyenes are produced by an unusual double-bond-shifting polyketide synthase. Expression of its gene is massively upregulated following mycelial damage. This study revealed that injury-induced de novo synthesis of polyketides is a fungal response strategy.

Other research highlights were achieved in the area of natural product biosynthesis, with focus on the enzyme mechanisms and the evolutionary origin of the biocatalysts. We have found that an important fungus used in food fermentation (*Aspergillus oryzae*) produces unusual aliphatic geminal dichloro compounds and that the major component of the complex (dichlorodiaporthin) is cytotoxic. Through functional gene analyses, *in vitro* biochemical assays and biotransformation experiments we have elucidated the molecular basis for dichlorination. We discovered and characterized an enzyme (AoiQ) that is unique because of the unprecedented marriage of a methyltransferase and a halogenase in one gene product. AoiQ also represents the first characterized fungal aliphatic halogenase, a novel flavoprotein that introduces halogens at a non-activated aliphatic carbon, and the first halogenase that catalyzes a regioselective dihalogenation of a freestanding substrate. Surprisingly, many genes for related hybrid enzymes were detected in the genomes of diverse ecologically relevant fungi. »

» OUR RESEARCH FOCUSES ON THE IDENTIFICATION AND INVESTIGATION OF PHARMACOLOGICALLY RELEVANT NATURAL PRODUCTS AS WELL AS VIRULENCE FACTORS IN MICROBES. COMBINING CHEMICAL AND BIOLOGICAL METHODS, WE EXPLORE NEW WAYS FOR DRUG DISCOVERY, ELUCIDATE BIOSYNTHETIC PATHWAYS AND STUDY ECOLOGICAL FUNCTIONS. «

Christian Hertweck

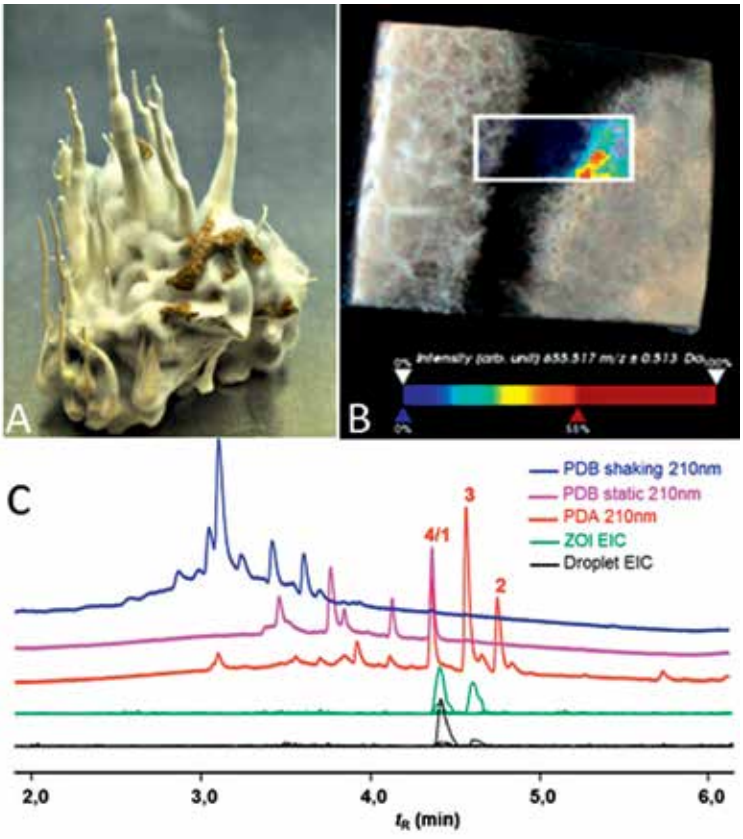

Figure 2: Top left: Fungus comb material from termites fungal garden overgrown by an opportunistic *Pseudoxylaria* sp.

Top right: Interaction assay of *Pseudoxylaria* sp. against co-isolate fungus *Coriolopsis* sp. Visualization of guttation droplets of *Pseudoxylaria* sp. using MALDI-TOF MS Imaging of *m/z* 655.517 +/− 0.513 Da ($[M+K]^+$ of Pseudoxylallemycin.

Bottom: HPLC chromatogram (210 nm) of cultivation conditions (PDB shaking, PDB static, PDA plates) and LC-MS chromatogram (EIC mode, Δ = 5.0 ppm) of secreted droplet (black) and zone of inhibition (ZOI, green).

In another study we have investigated an unusual enzyme catalyzing the key step towards the biosynthesis of a diverse family of antibiotics. Surprisingly, we found that this specialized enzyme has evolved from a widely distributed type of xenobiotic-detoxification enzyme. Specifically, we showed that an unusual indole oxygenase (XiaF) functions as a non-canonical terpenoid cyclase en route to xiamycin and congeners, which are active against various microorganisms including oomycetes. We unveiled a cryptic hydroxylation step that sets the basis for terpenoid cyclization. Biotransformation assays show that XiaF is a designated indole hydroxylase that can be used for the production of indigo and indirubin. The crystal structure of XiaF and phylogenetic analyses reveal that XiaF is, surprisingly, most closely related to xenobiotic-degrading enzymes. We provide a proof of concept for the evolution of biosynthetic pathways to antimicrobials from detoxification processes.

SELECTED COLLABORATIONS

Aspland, Simon
Acidophil LLC, Cambridge, UK

Bringmann, Gerhard
Julius Maximilians University Würzburg, Germany

Dittmann, Elke
University Potsdam, Germany

Fiebig, Heinz-Herbert
Oncotest GmbH, Freiburg, Germany

Groll, Michael
Technical University Munich, Germany

Kaltenpoth, Martin
Johannes Gutenberg University Mainz, Germany

Li, Ang
Chinese Academy of Sciences, Shanghai, China

Moore, Bradley
Scripps Institution for Oceanography, San Diego, USA

Müller, Rolf
Saarland University, Saarbrücken, Germany

Pidot, Sacha
University Melbourne, Australia

Sahl, Hans-Georg
Rheinische Friedrich Wilhelms University Bonn, Germany

Stehle, Thilo
Eberhard Karls University Tübingen, Germany

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MAJOR THIRD PARTY FUNDING

DFG: CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems – Project B1 and Coordination

DFG: Gottfried Wilhelm Leibniz Prize

InfectControl 2020: New antiinfection strategies – Science • Society • Economy – DrugBioTune

EU: Marie Sklodowska-Curie Actions – Individual Fellowship FUNBIT

Leibniz Competition: A Molecular Targeting Approach to Combat Human Pathogenic Fungi

DEPARTMENT

BIO PILOT PLANT

DEPARTMENT **BIO PILOT PLANT**

MOST IMPORTANT RESULTS

Droplet microfluidics for ultrahigh-throughput experimentation

We continued in developing our powerful, quantitative and miniaturized platform for future microbiological research based on droplet microfluidics.

Our major aim is to contribute to the urgent refilling of the antibiotic pipeline with novel chemical scaffolds by using this platform. The vast diversity of naturally occurring bacterial species can be harnessed by parallelized cultivation in pL droplets with an integrated screening for antibiotic substances. The cultivation outcome of the droplet-based microfluidic platform was tested for a microbial community derived from soil and compared to the cultivation outcome obtained by standard plating. Due to encapsulation of single cells in pL droplets, as an inherent advantage of the microfluidic platform, a broader set of microbes which are different to the set obtained on plates can be cultivated in droplets. Thereby more strains become available for a subsequent screening for antibiotic substances. The screening is based on whole cell reporter cells, which are pico injected into the droplets. After the assay was successfully validated it was used to identify and isolate several organisms in natural samples as putative producers of antimicrobial compounds. Among the gained isolate collection are several rarely isolated species and one candidate for a new species.

In order to expand into further microbiological applications, we integrated more functionalitites in the microfluidic platform. Besides applying the established in-droplet cultivation to various natural samples (soil and water) the incubation strategy was further extended from only gas control to pH control. To monitor the pH either in single droplets or for an entire droplet population a fluorescent dye was employed. By adding oil

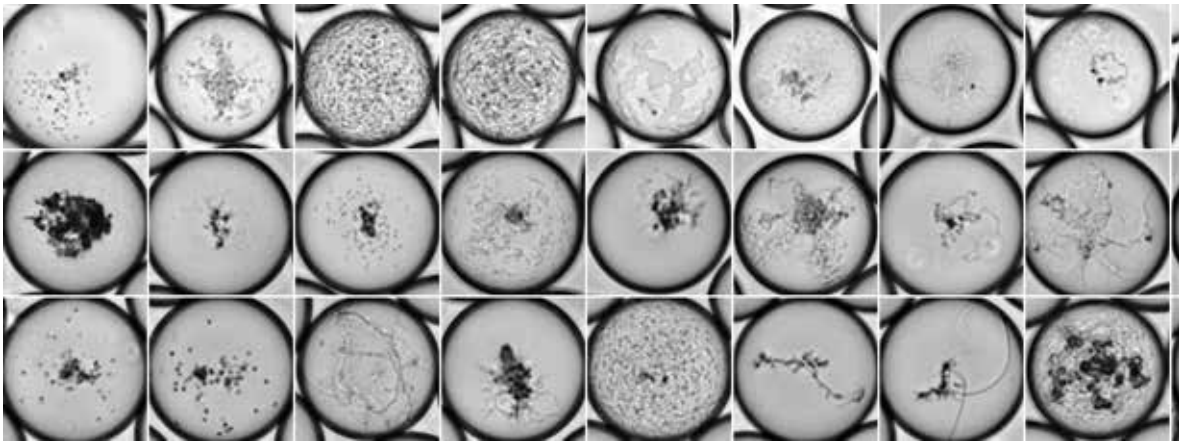


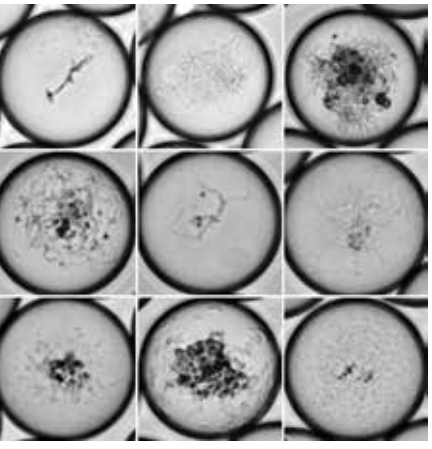
Figure 1: Species diversity observed in picolitre droplets. A microbial community derived from soil was encapsulated in 9 million droplets and incubated for a month under continuous and enhanced oxygen supply. The resulting species diversity of the grown cells was determined by sequencing the 16S rRNA gene.

» THE BIO PILOT PLANT USES INNOVATIVE TECHNOLOGIES FOR SCREENING OF LARGE AND DIVERSE POPULATIONS OF MICROBES TO SELECT PRODUCERS OF NOVEL ANTIMICROBIAL COMPOUNDS AND ENZYMES, AND DEVELOPS FERMENTATION AND DOWNSTREAM PROCESSES FOR PRODUCTION OF ANTIBIOTICS, ENZYMES, ANTIBODIES, TOXINS AND BIOPOLYMERS. «

Miriam Rosenbaum

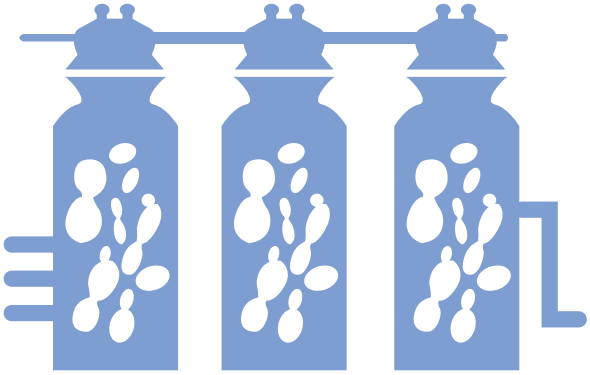
in which either a minute amount of an acid or a base is dissolved, the pH can be even actively changed, allowing sophisticated process control in droplets comparable to stirred bioreactors.

To expand the versatility of experimental conditions and samples that could be studied in droplet microfluidics, we have developed a new encoding method that tracks individual conditions inside large droplet populations (>10^5). The encoding approach is based on the encapsulation of a defined mixture of coloured beads together with biological samples in pL-droplets. For the decoding and detection of droplet content we developed an automated image-analysis-based method. We used this approach for analysis of bacterial susceptibility to antibiotics under 20 different experimental conditions simultaneously. Further technological advancements comprise a multi-wavelength detection system, capable of simultaneously detecting four different fluorescence colours using a single detector. This enables multi-parametric measurements in various microbiological and bioanalytical studies, e. g. co-cultivation, and multivariable cytometry. Optical elements have been replaced with optical fibers which makes the overall microfluidic detection system simple, flexible, low-cost and compact. Additional developments include an automatic valve-switching system for controlling absolute numbers of droplets, a method for easier production of complex chip architectures, capable of fiber integration or pseudo-3D structures, and electronic improvements.



Novel antibody formats for diagnostics

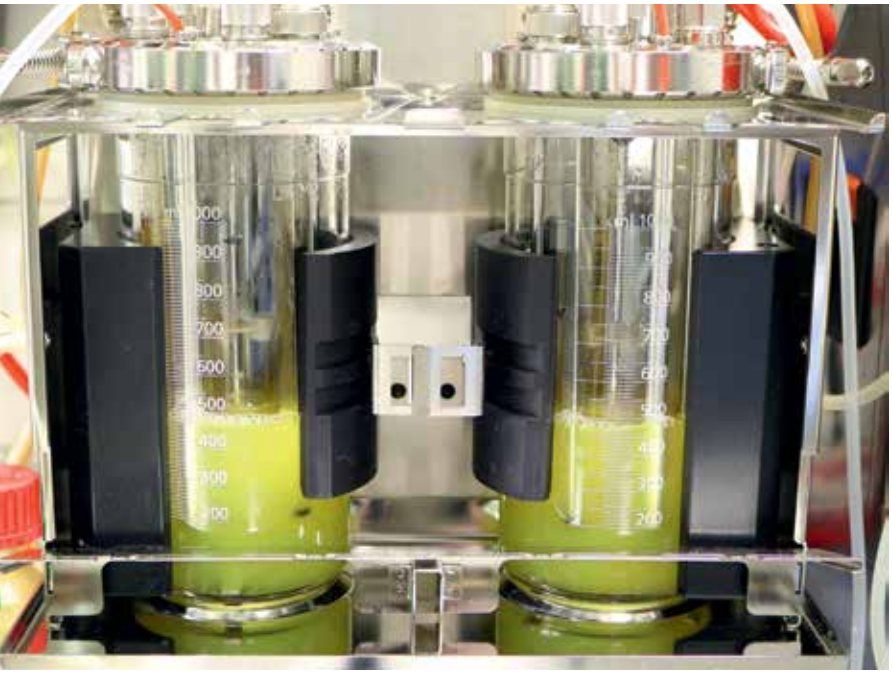
New therapies and diagnostics have a high demand of recombinant antibodies. Efficient expression systems are needed for the production of the antibodies. However, the concentration of target proteins in inclusion bodies implies the risk of losing the biological function caused by renaturation and refolding procedures. There- »



fore the optimization of production processes and especially the downstream processing is a challenge. In collaboration with an industrial partner upstream and downstream processes for the production of biologically active proteins were analyzed to improve the process scalability and the yield of soluble and biologically active protein.

The recombinant production of VHH antibodies in *E.coli* is of great advantage in development of new therapeutic and diagnostic strategies. In contrast to the production of mono- and polyclonal antibodies, it is possible to generate time and cost efficiently a high amount of VHH antibodies by high cell density fermentation. Due to easy genetic modification, VHH antibodies can be adapted to different medical applications. We developed VHH antibodies for detection of specific biomarkers in sepsis diagnostics and proteins in terms of AA amyloidosis.

Figure 2: Colourful natural products produced by an anaerobic *Clostridium* species grown in bioreactors.



Secondary metabolites from anaerobic and other neglected bacteria

Current genome mining approaches (department Biomolecular Chemistry) revealed the potential of anaerobic bacteria to produce so far unknown secondary metabolites. Especially non-pathogenic, solventogenic and cellulolytic clostridia possess the genetic basis to produce novel natural products with pharmaceutical activities and environmental importance. In lab-scale bioreactors (1-7 L) several strictly anaerobic clostridia strains were cultured under defined culture conditions to screen for new metabolites. Relevant gene clusters were knocked out using the ClosTron mutagenesis system. Knockout mutants were analyzed for phenotypic and metabolic changes to identify the biological and environmental role of these substances. So far, this screening approach has resulted in the isolation and characterization of a novel long-chain N-acyl amino acid antibiotic.

The Bio Pilot Plant supported the junior research groups Chemistry of Microbial Communication and Chemical Biology of Microbe-Host Interactions by performing fermentations of diverse microorganisms and downstream processing in order to enable the isolation and structure elucidation of new natural products, e. g. pyreudiones, rubterolones, and anikasin. In addition the essential taxonomic description of isolated novel microbes was done in cooperation.

SELECTED COLLABORATIONS

Becker, Tino
LaCoSys GmbH, Jena, Germany

Beckert, Erik
Fraunhofer Institute for Applied Optics and Precision Engineering, Jena, Germany

Czerney, Peter
Dyomics GmbH, Jena, Germany

Driesch, Dominik
BioControl Jena GmbH, Jena, Germany

Kämpfer, Peter
Justus Liebig University Gießen, Germany

König, Gabriele
Rheinische Friedrich Wilhelms University Bonn, Germany

Martin, David
Tepha Inc., Lexington, USA

Müller, Rolf
Saarland University, Saarbrücken, Germany

Sahl, Hans-Georg
University Hospital Bonn, Germany

Seise, Enrico
Invigon GmbH, Jena, Germany

Thomas, Oetzel
Merck KGaA, Darmstadt, Germany

Ziemert, Nadine
Eberhard Karls University of Tübingen, Germany

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Funk J, Schaarschmidt B, Slesiona S, Hallström T, Horn U, Brock M (2016) The glycolytic enzyme enolase represents a plasminogen-binding protein on the surface of a wide variety of medically important fungal species. *Int J Med Microbiol* 306, 59-68.

Wulff M, Baumann M, Thümmler A, Yadav JK, Heinrich L, Knüpfer U, Schlenzig D, Schierhorn A, Rahfeld JU, Horn U, Balbach J, Demuth HU, Fändrich M (2016) Enhanced fibril fragmentation of N-terminally truncated and pyroglutamyl-modified Aβ peptides. *Angew Chem Int Ed Engl* 55, 5081-5084.

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Klapper M, Götze S, Barnett R, Willing K, Stallforth P (2016) Bacterial alkaloids prevent amoebal predation. *Angew Chem Int Ed* 55, 8944-8947.

Walther E, Boldt S, Kage H, Lauterbach T, Martin K, Roth M, Sauerbrei A, Hertweck C, Schmidtke M, Nett M (2016) Zincophorin – biosynthesis in *Streptomyces griseus* and antibiotic properties. *GMS Infect Dis* 4, doc08.

MAJOR THIRD PARTY FUNDING

Free State of Thuringia (EFRE): DropCode: Microfluidic platform technology for ultra-high throughput screening of novel antimicrobial compounds from microorganisms

DZIF: Collaborative project TTU 09.811 – Innovative microbial resources for new anti-infectives

by Tepha Medical Devices, USA: Development and optimization of fermentation and downstream processes for the production of polyhydroxyalkanoates for medical applications

DEPARTMENT

CELL AND MOLECULAR BIOLOGY

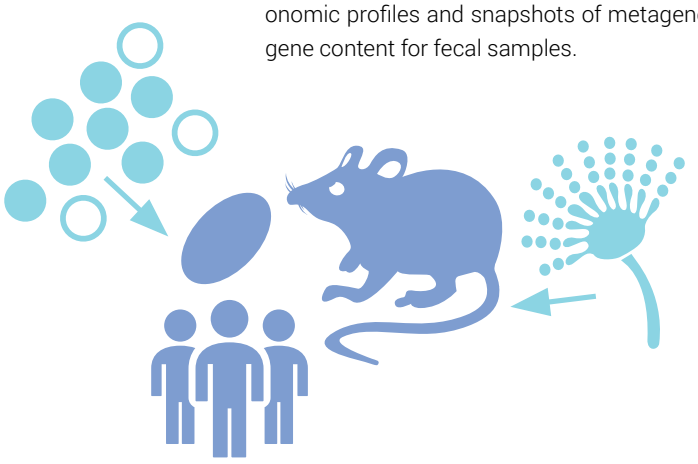

BGR 500

DEPARTMENT
CELL AND MOLECULAR BIOLOGY

MOST IMPORTANT RESULTS

Microbiome-host interactions

These studies concerned the taxonomic and functional characterisation of the microbial gut communities in economically and alimentary relevant marine organisms in Indonesian coastal areas under pollutant and non-pollutant conditions. The microbiome included bacterial, fungal, protistan, and viral species, many of which pose threats to human and animal health, and/or impact sustainability of food production. By employing culture-independent metagenomic and microbiomic approaches, we generated taxonomic profiles and snapshots of metagenome gene content for fecal samples.



Aspergillus fumigatus infection and its role during host cell apoptosis

Using hyperspectral imaging we showed that melanin of *A. fumigatus* conidia has the ability to interfere with the apoptosis process in human monocytes by enabeling the apoptotic cells to recover from mitochondrial acidification and thus to continue their life cycle.

In vivo quantification of experimental arthritis by PET/CT imaging

The assessment of bone damage is required to evaluate disease severity and treatment efficacy both in arthritis patients and in experimental arthritis models. Today, there is still a lack of *in vivo* methods that enable fast and objective quantification of arthritic processes at an early stage of the disease. Therefore, we performed longitudinal *in vivo* imaging with ^{18}F-fluoride PET/CT and developed routines for automated image analysis to assess pathological bone turnover and bone destruction in an experimental model of arthritis. The uptake of the bone-seeking tracer ^{18}F-fluoride was significantly increased in fore- and hind-paws of diseased animals and specific for sites of active arthritis manifestation. Automated analysis of high-resolution CT images was performed to quantify the degree of bone damage longitudinally throughout the course of the disease. Especially bone surface roughness turned out to be highly sensitive for early bone destruction (Fig. 1). Furthermore, this approach was able to detect clear differences in alterations of the bone surfaces at periosteal and endosteal sites of the bones. These differences indicate that the roughness analysis is capable of recognition of bone erosion as well as new bone formation, depending on the respective parameters used for image analysis. Together with PET imaging, this approach allows to reduce the number of animals needed in a study while providing longitudinal insights into metabolic and anatomical changes in experimental arthritis.

High-intensity UV laser ChIP-seq for the study of protein-DNA interactions in living cells

Genome-wide mapping of transcription factor binding is generally performed by chemical protein-DNA crosslinking, followed by chromatin immunoprecipitation and deep sequencing (ChIP-Seq). Although the conventional studies have yielded many important insights, several relevant limitations have been identified. Formaldehyde crosslinking is relatively slow and generates protein-protein and protein-DNA formations, thus disallowing for the discrimination between direct and indirect DNA interactions. Protein-protein crosslinking may lead to the identification of artefactual protein-DNA binding, in particular at highly accessible loci. Formaldehyde treatment can cause the destruction or masking of epitopes and is known to affect the sensitivity of chromatin to fragmentation. In addition, highly dynamic protein-DNA interactions might become undetectable through formaldehyde based ChIP.

For these reasons, we developed the ChIP-seq method based on photochemical protein-DNA crosslinking by high-intensity nanosecond-pulsed ultraviolet (UV) laser irradiation, which provides the researcher with a "snapshot" of the highly complex natural state of specific and direct protein-DNA interactions in living cells (Fig. 2). As model system we have chosen the well-known transcription factor BCL6 in human lymphoma B-cells, which interacts with specific DNA recognition elements within the genome. Thereby, our technique enabled the accurate and precise discovery of many previously undetectable direct BCL6 binding sites, particularly in condensed, inaccessible areas of chromatin. »

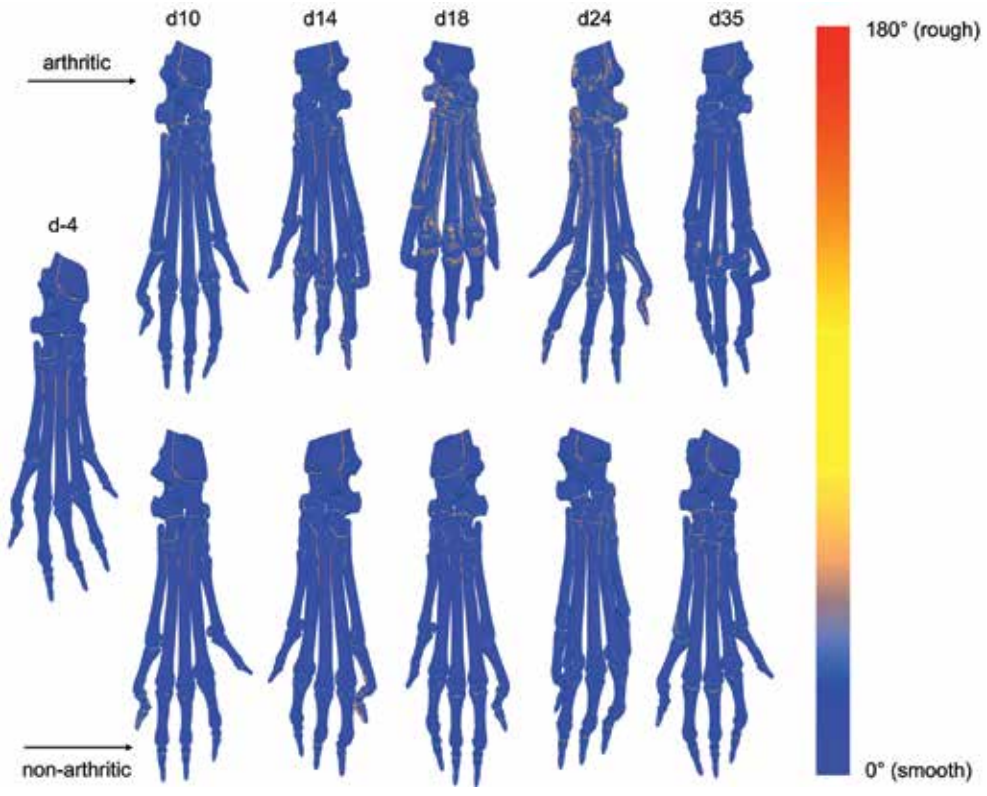
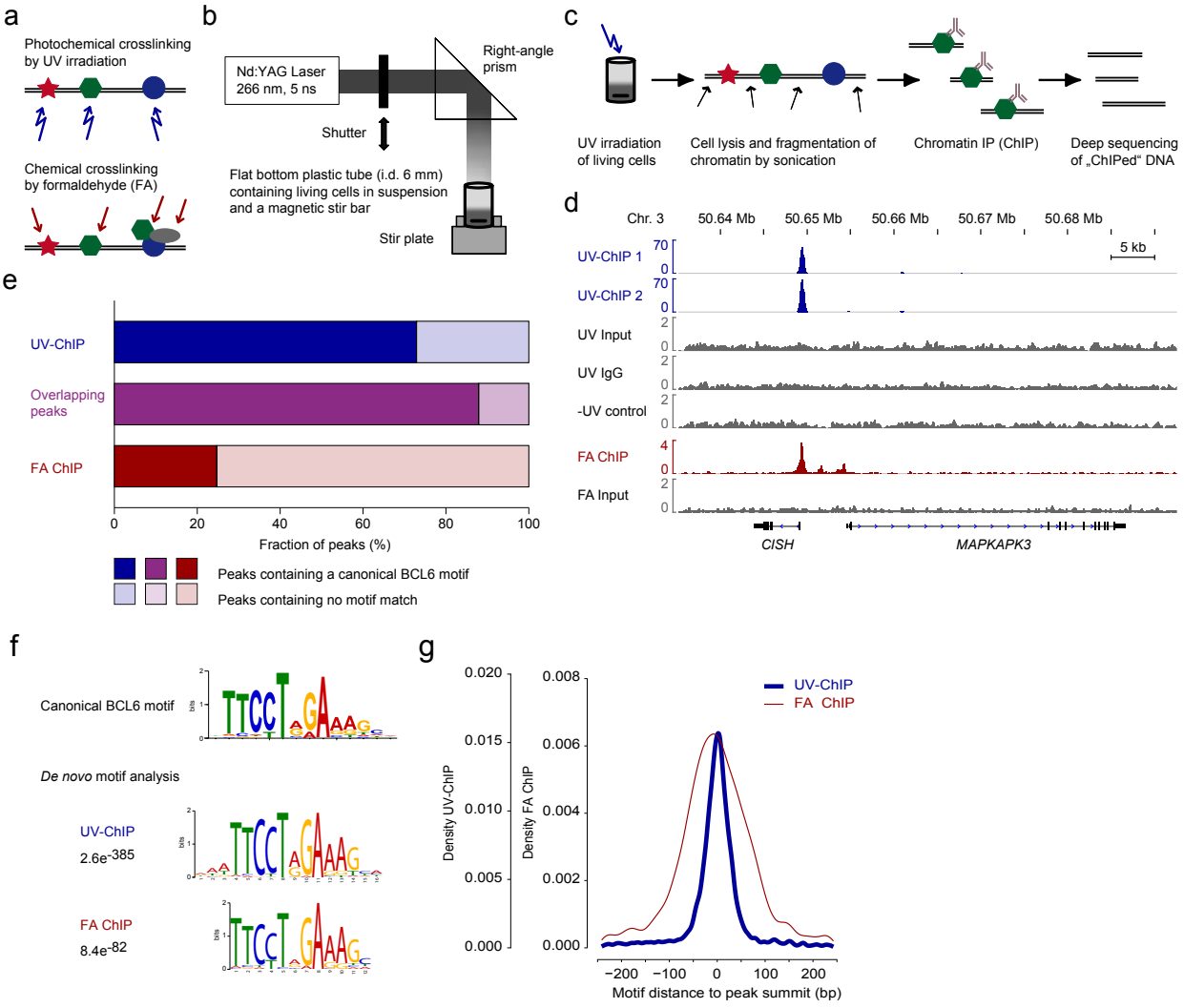


Figure 1: Visualization of bone surface roughness of arthritic (top row) and healthy (bottom row) mouse hind-paws over time. A gradient from blue color (smooth regions) to red color (rough regions) indicates erosion of the bone surface in arthritic animals.



Mass spectrometry imaging

The chemical analysis of biological tissues with three-dimensional shapes has been a major problem so far. In cooperation with scientists from the Max Planck Institute for Chemical Ecology and the Fraunhofer Institute for Applied Optics and Precision Engineering in Jena, Germany, we established a mass spectrometry imaging approach in such a way that the distribution of molecules can also be visualized on rippled, hairy, bulgy or coarse surfaces. The laser-based equipment was custom-built to accommodate the topography of non-flat samples. The stability of the system was evaluated by the metabolic profiling of radish leaves, chosen due to their distinct surface nature and known metabolites.

Figure 2: High-intensity UV-ChIP-seq for the study of BCL6-DNA interactions. (a) Crosslinking strategies. Photochemical crosslinking by UV irradiation results in the formation of covalent "zero-length" protein-DNA crosslinks. Chemical crosslinking by formaldehyde (FA) fixates protein-protein and protein-DNA interactions via methylene bridges. (b) Experimental setup for high-intensity UV laser irradiation of living cells. (c) UV-ChIP-seq workflow. (d) ChIP-seq profiles of an example region containing a validated BCL6 binding site. Read density profiles of BCL6 UV-ChIP-seq (UV-ChIP 1 and 2, blue tracks) and UV control (UV input DNA, UV IgG control and -UV control ChIP, grey tracks) data are shown for the human CISH, MAPKAPK3 loci. UV-ChIP-seq detects specific enrichment within the promoter region of the CISH gene, overlapping the canonical BCL6 motif previously found by FA ChIP-seq (red track). (e) Occurrence of canonical BCL6 motifs within detected peaks. The fraction of peaks (%) containing a canonical BCL6 motif (q-value 0.1, dark colored) and the fraction that do not contain a BCL6 motif match (light colored) are plotted for UV-ChIP-seq (72.9% peaks with motif, blue), FA ChIP-seq (24.7%, red) and overlapping binding sites (88.0%, purple). (f) DNA sequence motif analysis. The canonical BCL6 motif and the corresponding de novo DNA sequence motifs discovered from UV- and FA ChIP-seq data analyses are shown and E-values are indicated. (g) Distance of BCL6 motifs relative to peak summits. The distance of canonical BCL6 motifs is plotted relative to the corresponding peak summit (base position of maximum enrichment, x axis, ± 250 bp) as detected by UV-ChIP-seq (blue) and FA ChIP-seq (red).

» RESEARCH IN OUR DEPARTMENT IS MAINLY DEVOTED TO THE FLOW OF MOLECULAR INFORMATION DURING HOST-PATHOGEN INTERACTIONS. TO CAPTURE PATHOGEN- AND HOST-SPECIFIC ASPECTS EFFECTIVELY, WE ALSO ADOPT AND DEVELOP HIGHLY ADVANCED MOLECULAR TECHNIQUES, WHICH ALLOW THE STUDY OF YET UNKNOWN RELEVANT QUESTIONS. «

Hans Peter Saluz

SELECTED COLLABORATIONS

Dsikowitzki, Larissa
RWTH Aachen University, Aachen, Germany

Ehlbeck, Jörg
Leibniz Institute for Plasma Science and Technology, Greifswald, Germany

Palm, Harry
University of Rostock, Germany

Sauerbrei, Andreas
Friedrich Schiller University Jena , Germany

Schmidtke, Michaela
Friedrich Schiller University Jena , Germany

Schultz, Claudia
Leibniz Centre for Tropical Marine Research, Bremen, Germany

Svatos, Ales
Max Planck Institute for Chemical Ecology, Jena, Germany

Walther, Elisabeth
Friedrich Schiller University Jena, Germany

Weyers, Markus
Ferdinand-Braun-Institut, Leibniz-Institut für Höchstfrequenztechnik, Berlin, Germany

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Hennersdorf P, Mrotzek G, Abdul-Aziz MA, Saluz HP (2016) Metagenomic analysis between free-living and cultured *Epinephelus fuscoguttatus* under different environmental conditions in Indonesian waters. *Mar Pollut Bull* 110, 726-734.

Hoffmann B, Svensson C.-M, Straßburger M, Gebser B, Irmler IM, Kamradt T, Saluz HP, Figge MT (2017) Automated quantification of early bone alterations and pathological bone turnover in experimental arthritis by *in vivo* PET/CT imaging. *Sci Rep* 7, 2217.

Svensson C-M, Hoffmann B, Irmler IM, Straßburger M, Figge MT, Saluz HP (2017) Quantification of arthritic bone degradation by analysis of 3D micro-computed tomography data. *Sci Rep* 7, 44434.

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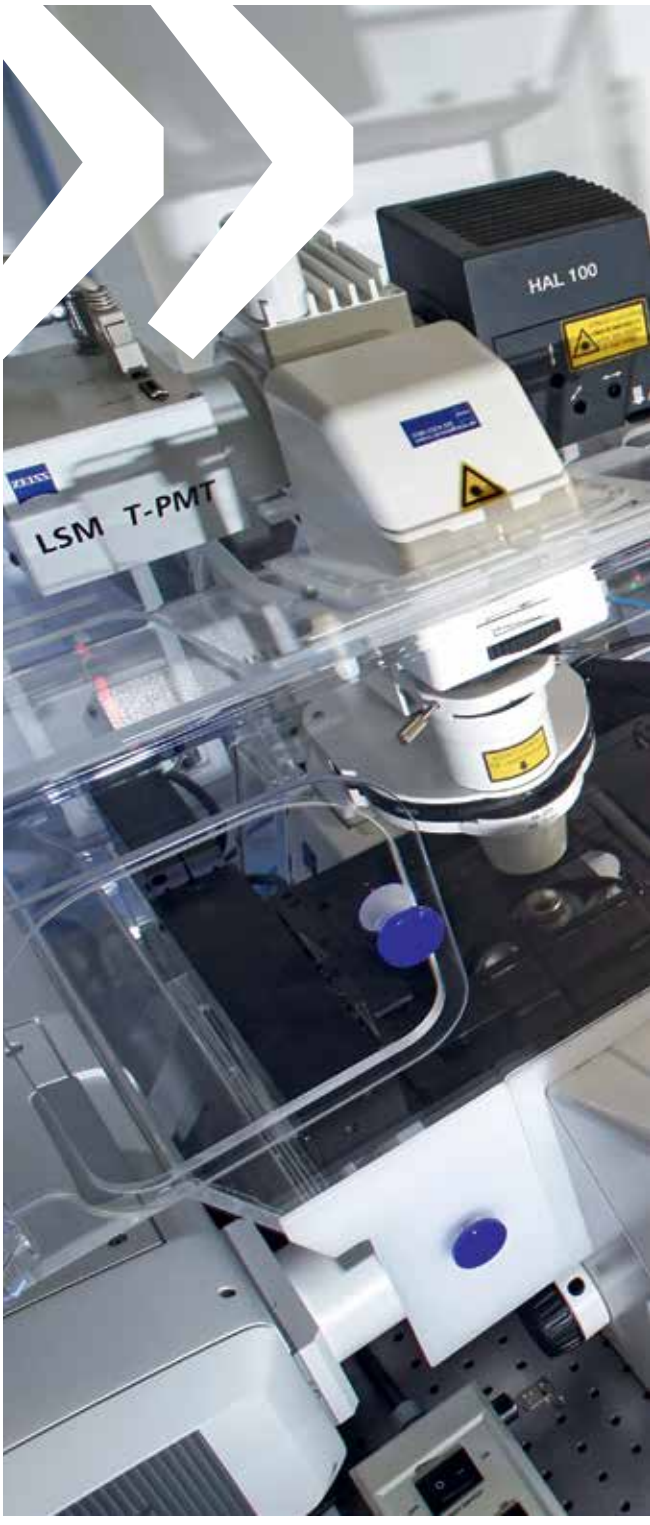
Bartels B, Kulkarni P, Danz N, Böcker S, Saluz HP, Svatoš A (2017) Mapping metabolites from rough terrain: laser ablation electrospray ionization on non-flat samples. *RSC Adv* 7, 9045-9050.

MAJOR THIRD PARTY FUNDING

BMBF: Advanced UV for Life – StaFluKo-MNO

DEPARTMENT

INFECTION BIOLOGY



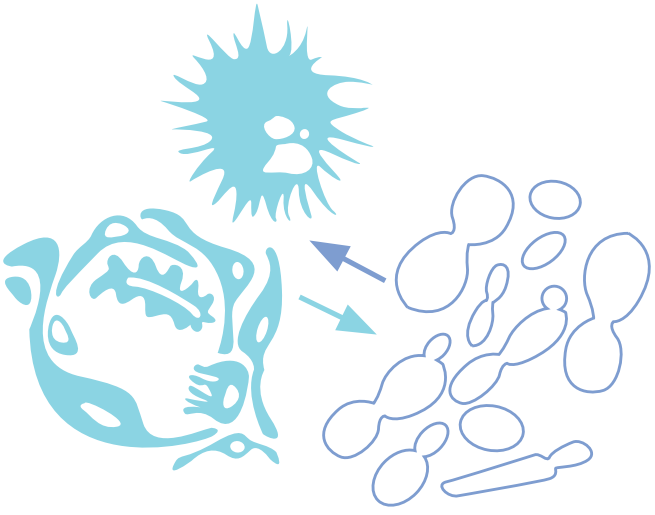
DEPARTMENT **INFECTION BIOLOGY**

MOST IMPORTANT RESULTS

The Department Infection Biology analyses the role of the complement system in health and diseases. Complement was initially identified as a defense system of innate immunity that targets and eliminates foreign infectious microbes. Modern complement research shows that this system in addition maintains homeostasis and coordinates innate and adaptive immunity. The work of the Department Infection Biology focuses on immune evasion of pathogenic microbes, in particular of human pathogenic fungi, such as *Candida albicans* and on the homoeotic functions of complement in mediating kidney integrity.

Candida albicans, *Aspergillus fumigatus* and many other pathogenic microbes have learned throughout evolution to avoid recognition and to counteract destruction by the host complement system. The human pathogens mimic surfaces of host cells and bind protective regulators from human plasma. We identify such immune interactions by isolating the corresponding fungal immune evasion proteins and studying their interaction with human immune regulators including Factor H, the FHR proteins and Plasminogen. Plasminogen attached to either the purified proteins or to the fungal pathogens is accessible for activators and can be converted to the active protease plasmin. Active plasmin then damages host endothelial cells and epithelial cells and induces cell retraction, exposure of the subcellular matrix and further degradation of matrix components. Such local tissue damage ultimately helps the pathogenic microbe to cross host tissue barriers and to disseminate into deeper tissue layers.

We identified Pra1, the pH-regulated antigen, which is a multifunctional immune evasion protein of the human pathogenic yeast *C. albicans*, as a hierarchical complement inhibitor that targets C3, the central human complement component. Pra1 cleaves C3 at a unique site and further inhibits effector functions of the activation fragments. The newly formed C3a-like peptide lacks the C-terminal arginine residue needed for C3a-receptor binding and activation. Moreover, Pra1 blocks C3a-like antifungal activity as shown in survival assays, and the C3b-like molecule formed by Pra1 is degraded by the host protease Factor I. Pra1 also binds to C3a and C3b generated by human convertases and blocks their effector functions. In addition, it inhibits C3a antifungal activity and blocks C3a binding to human



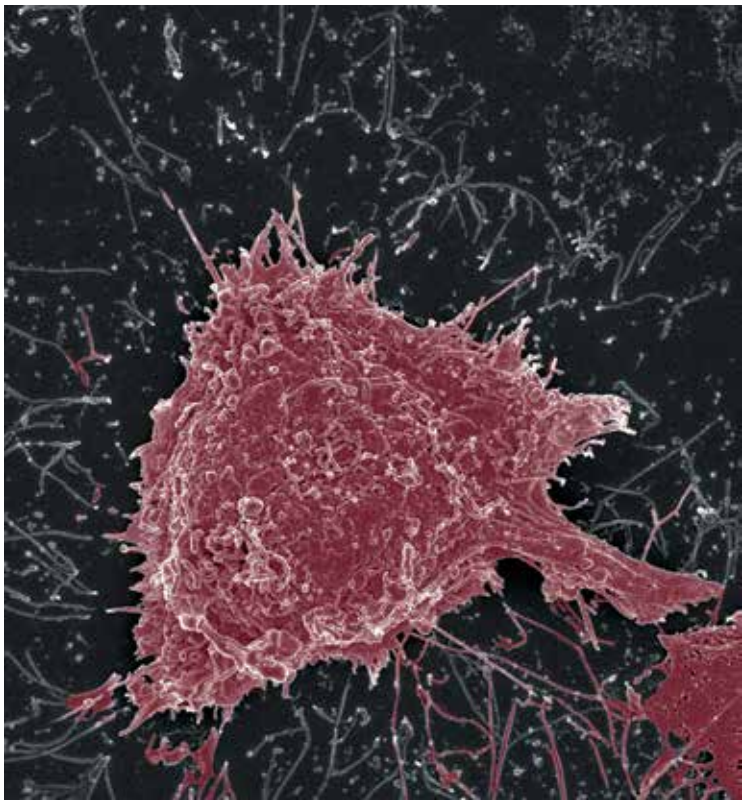


Figure 1: Clinical pneumococci isolates which have active protease plasmin attached to their surface damage human endothelial cells.

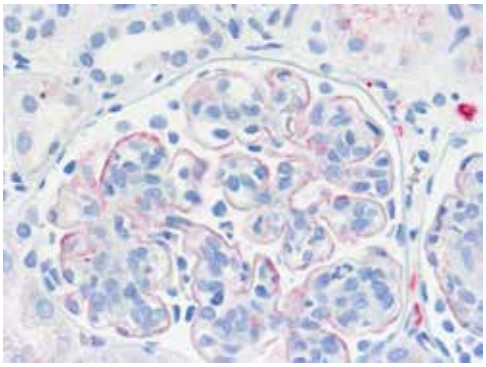
The protease plasmin bound to the surface of *Streptococcus pneumoniae* damages human endothelial monolayer, induces cell retraction and exposure of the sub endothelial matrix. Electron microscopy images generated by Dr. Martin Westermann, Center for Electron Microscopy, University Hospital Jena.

C3a receptor-expressing expressing HEK cells. It prevents activation of Fura2-AM loaded cells, intracellular Ca^{2+} signaling, IL-8 release, C3b deposition, as well as opsonophagocytosis and killing by human neutrophils. Thus, upon infection *C. albicans* uses Pra1 to destroy C3 and to disrupt host complement attack. In conclusion, Pra1 represents the first fungal C3-cleaving protease identified and functions as a fungal master regulator of innate immunity and as a central fungal immune-escape protein.

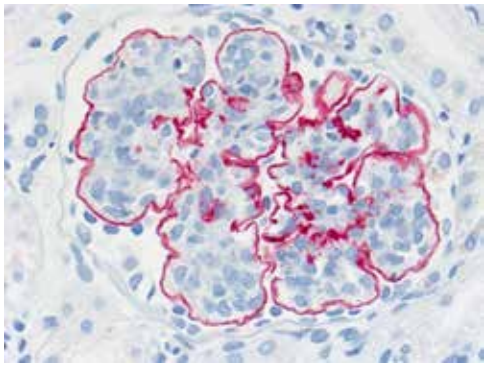
The immune evasion mechanisms of pathogenic microbes by means of the immune evasion proteins PspC derived from clinical *Streptococcus pneumoniae* were studied. *Streptococcus pneumoniae* isolates from children with pneumococcal hemolytic uremic syndrome (HUS) expressed unique PspC variants. Because endothelial cell damage is a hallmark of HUS, we studied how HUS-inducing pneumococci derived from these infant HUS patients during the acute phase disrupt the endothelial layer. These clinical isolates of HUS pneumococci efficiently bound human plasminogen via the bacterial surface proteins, Tuf and PspC. PspC is a pneumococcal plasminogen. When activated at the bacterial surface the active protease plasmin degrades fibrinogen and cleaves C3b. Thereby PspC bound plasmin attached to the clinical HUS pneumococci damaged endothelial cells, caused endothelial retraction and exposure of the underlying matrix. Thus, HUS pneumococci damage endothelial cells in the blood vessels and disturb local complement homeostasis. Thereby, HUS pneumococci promote a thrombogenic state that drives HUS pathology.

C3 glomerulopathy (C3G) represents a severe kidney disease for which at present no specific therapy exists. The causes of C3G are heterogeneous and defective complement regulation is often linked to pathogenesis. Copy number variations in the CFHR gene cluster on chromosome 1q32 and CFHR5 mutant proteins are associated with this severe kidney disease. Here, we identify CFHR5 as a new pattern recognition protein that binds to damaged self surfaces and anchors properdin, the human complement activator, to such modified sites.

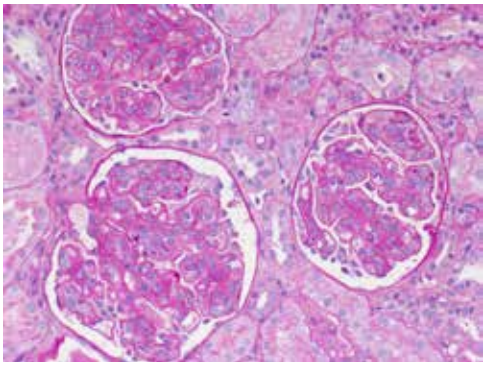
Hybrid FHR proteins cause kidney damage in form of CFHR glomerulonephritis. This disease association initiated the interest in understanding the biological role of FHR5 and the disease pathology of FHR2::FHR5 hybrid mutants. To this end we analyzed the domain organization of the FHR5 protein. The N-terminal two SCR domains of FHR5 contact properdin and are also relevant for dimer formation. Two mutant CFHR5 proteins, FHR2-FHR5Hyb derived from German and FRH5Dup from Cypriot C3G patients have these properdin binding segments duplicated. The mutants FHR2-FHR5Hyb and the FRH5Dup with the duplicated SCRs1, 2 assemble to large »



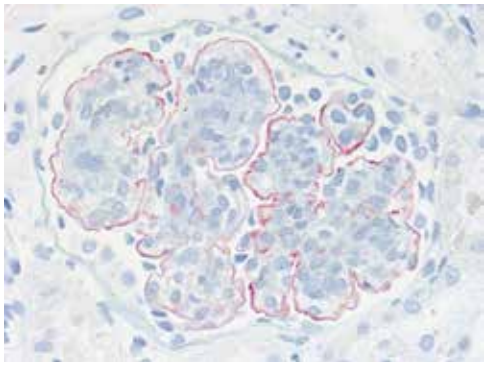
CFHR2



CFHR5



PAS



Properdin

Figure 2: The complement proteins FHR2 and FHR5 are deposited in kidneys of C3Glomerulopahty patients. Protein deposition is detected along the glomerular basement membrane and in the mesangial area. PAS staining shows the structure of kidney glomeruli and properdin the complement activator is also deposited at the glomerular basement membrane. Images performed by Prof. Thorsten Wiech University Hospital Hamburg

multimeric complexes, bind much stronger to modified self surfaces, enhance properdin attachment and exacerbate local complement activation. Such enhanced surface binding and properdin recruitment is relevant *in vivo* within mesangial cells of a transplanted and explanted kidney from the German C3G patient who expressed the CFHR2-CFHR5Hyb protein. Such enhanced properdin staining correlates with local complement activation and C3b and C5b-9 deposition. This gain-of-function of two related disease associated CFHR5 mutants for local complement action describes a new disease mechanism of C3G glomerulopathy which is relevant to define appropriate treatment options for this severe kidney disorder.

» THE DEPARTMENT INFECTION BIOLOGY ANALYSES THE COMPLEMENT SYSTEM IN HEALTH AND DISEASE. OUR WORK FOCUSES ON IMMUNE EVASION OF PATHOGENIC MICROBES, IN PARTICULAR OF HUMAN PATHOGENIC FUNGI, SUCH AS *CANDIDA ALBICANS*, AND ON THE HOMEOTIC FUNCTIONS OF COMPLEMENT IN MEDIATING KIDNEY INTEGRITY. «

Peter F. Zipfel

SELECTED COLLABORATIONS

Andersen, Gregers R.
University of Aarhus, Denmark

Binder, Christoph J.
Medical University of Vienna, Austria

Engelmann, Susanne
Technical University Braunschweig, Germany

Fremeaux-Bacci, Veronique
Hôpital européen Georges-Pompidou, Paris, France

Hammerschmidt, Sven
University Greifswald, Germany

Kraiczy, Peter
Johann Wolfgang Goethe University Frankfurt, Germany

Pradel, Gabriele
RWTH Aachen University, Aachen, Germany

Ram, Sanjay
Boston University, Boston, USA

Remuzzi, Giuseppe
Istituto di Ricerche Farmacologiche "Mario Negri", Bergamo, Italien

Riesbeck, Kristian
Lund University, Malmö, Schweden

Wallich, Reinhard
Ruprecht Karls University Heidelberg, Germany

Wiech, Thorsten
University Hospital Hamburg, Germany

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Chen Q, Manzke M, Hartmann A, Büttner M, Amann K, Pauly D, Wiesener M, Skerka C, Zipfel PF (2016) Complement Factor H Related 5-Hybrid proteins anchor properdin and activate complement at self-surfaces. *J Am Soc Nephrol* 27, 1413-1425.

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Micklisch S, Lin Y, Jacob S, Karlstetter M, Dannhausen K, Dasari P, von der Heide M, Dahse HM, Schmölz L, Grassmann F, Alene M, Fauser S, Neumann H, Lorkowski S, Pauly D, Weber BH, Joussen AM, Langmann T, Zipfel PF, Skerka C (2017) Age-related macular degeneration associated polymorphism rs10490924 in ARMS2 results in deficiency of a complement activator. *J Neuroinflammation* 14(1), 4.

Pollmächer J, Timme T, Schuster S, Brakhage AA, Zipfel PF, Figge MT (2016) Deciphering the counterplay of *Aspergillus fumigatus* infection and host inflammation by evolutionary games on graphs. *Sci Rep* 6, 27807.

MAJOR THIRD PARTY FUNDING

DFG: CRC 1192 Immune-Mediated Glomerular Diseases – Project B6

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project C4

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project C6

DFG: Die Faktor H-vermittelte Komplementevasion des Malariaparasiten *Plasmodium falciparum*

DEPARTMENT

MICROBIAL PATHOGENICITY MECHANISMS

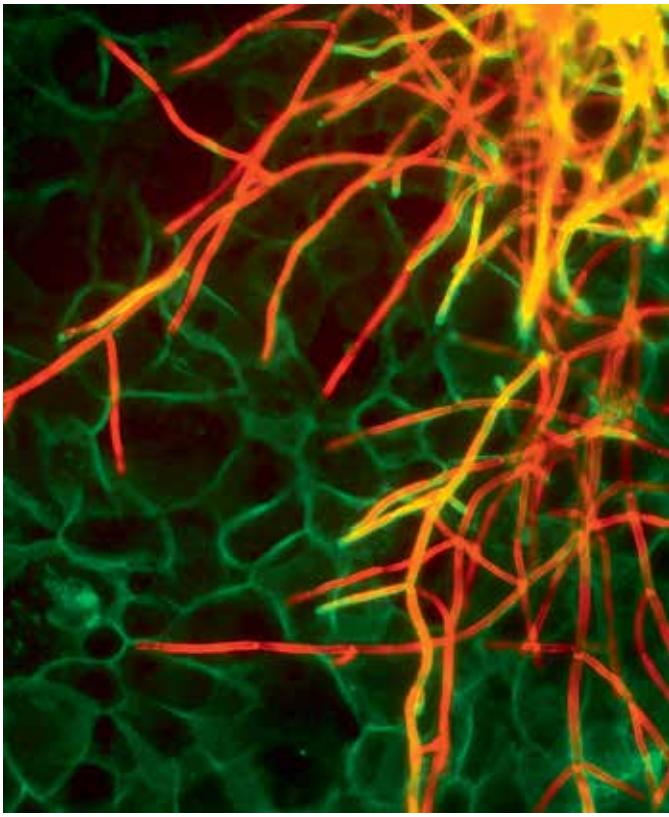

100 ml

DEPARTMENT
MICROBIAL PATHOGENICITY MECHANISMS

MOST IMPORTANT RESULTS

Our research of the years 2016 and 2017 has been predominantly characterized by two major lines of inquiry: 1) Role of a secreted peptide toxin – Candidalysin – in *Candida albicans* pathogenicity; and 2) Networks of micronutrient acquisition during *Candida* infections.

(1) *Candida albicans* pathogenicity has long been linked to its ability to form hyphae, and this morphological state has frequently been associated with infections ranging from superficial to systemic and even sepsis. What makes hyphae so important in pathogenicity, compared to the yeast morphological form, was, however, not completely understood: On the one hand hyphae are more adhesive and invasive on both biotic and abiotic surfaces, and this was often thought to sufficiently explain the different pathogenic potential of the two morphologies. But hyphae, or hyphae-associated processes, were also known to trigger an inflammatory response able to specifically sense pathogenic *C. albicans* – a "danger response" capable of discriminating between yeast and hyphal growth. To differentiate whether hyphae per se or hypha-associated factors are responsible for the "danger response", we performed, in collaboration with Prof. Julian Naglik and his team at the King's College in London (UK), a screening of a set of mutants that lack genes linked with filamentation. We evaluated markers of the "danger response", including the ability of the strains to cause damage to host cells. Of all the mutants tested, those that were unable to filament were consistently also unable to trigger the danger response, whereas all strains that were able to filament were fully able to do so – all except one. This strain lacks the ECE1 gene, which we later discovered to encode a peptide toxin that is secreted by invading hyphae and which we found to be critical for mucosal infection. Due to its ability to lyse host cells we named this toxin "Candidalysin", the first of its kind discovered in a human pathogenic fungus. "ECE1 and Candidalysin" have since become a major driving topic in our laboratory, putting us and our collabora-



» USING CELLULAR, MICROBIAL, MOLECULAR AND BIOCHEMICAL METHODS AND *CANDIDA ALBICANS* AND *C. GLABRATA* AS MODEL ORGANISMS, THE GOAL OF OUR RESEARCH IS TO UNDERSTAND HOW HUMAN PATHOGENIC YEASTS CAUSE DISEASE. «

Bernhard Hube

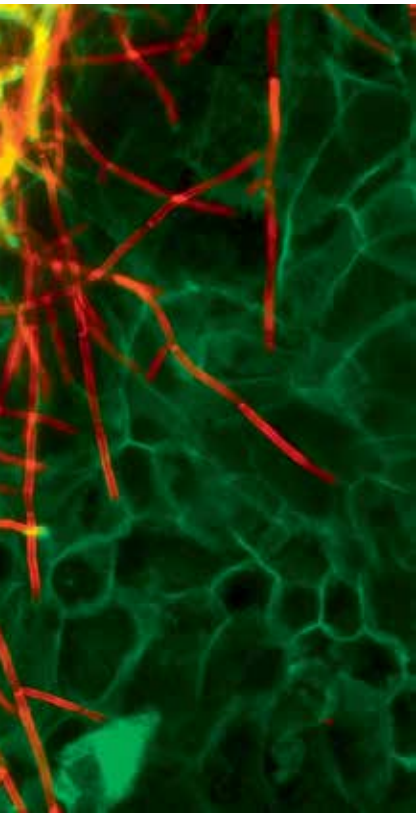
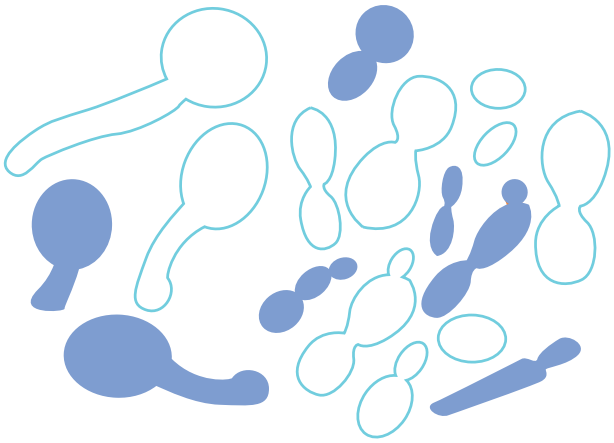


Figure 1: *C. albicans* hyphae invade into human epithelium (red hyphae) or grow on its surface (yellow hyphae). Cover photograph – *Eukaryotic Cell* 2014 Aug;13(8) (Copyright © 2014, American Society for Microbiology)

tion partners in a world-leading position in this new aspect of *Candida* pathogenity. In collaboration with Prof. Sarah Gaffen, University of Pittsburgh (USA), and other long standing collaborators, we have recently published another major finding on Candidalysin: We found that the innate immune response, which is predominantly orchestrated by IL-17 producing cells during *C. albicans* pathogenicity, is triggered by *C. albicans* hyphae more than by yeasts due to their Candidalysin secretion. While this was demonstrated in oral epithelial cells, other cell types are similarly affected by Candidalysin, including vaginal epithelia. This way the toxin exacerbates immunopathogenesis of *C. albicans* vaginitis, the most common manifestation of *C. albicans* infections.

(2) Damage to the host is, however, not a self-serving event during pathogenesis, but is rather required by pathogens to obtain nutrients during infections. Among the arguably most limited nutrients in the host are different metals, and in the past we have investigated how *C. albicans* can acquire iron or zinc from different host molecules. In fact, the active limitation of metal availability is a long-recognized phenomenon, frequently called nutritional immunity, and the study and disruption of the pathogen's countermeasures is considered a promising avenue to the development of new treatment options. We have focused mainly on *C. glabrata* in this research period. Among our most important results is the new finding that *C. glabrata* seems to use a unique regulatory network to respond to iron abundance in its environment. As a yeast with a close evolutionary relationship with *Saccharomyces cerevisiae*, we expected this pathogen to employ the unusual and – in comparison to other fungi – newly developed regulatory system of baker's yeast. Indeed we found that both species rely mainly on the same transcription factor, Aft1, to regulate iron homeostasis, but *C. glabrata* shows important deviations from this network. Our research revealed a hybrid regulatory network in *C. glabrata*, which combines features from both harmless baker's yeast and pathogenic fungal species. In the same vein, we found that *C. glabrata* differs from other pathogenic fungi in its absence of surface ferric reductases. These enzymes normally allow efficient iron uptake even under severely limited conditions as encountered in the host. Consequently, fungi like *C. albicans* have large gene families of these reductases at their disposal. Again, *C. glabrata* follows a seemingly unique »



strategy among pathogenic yeasts by employing a soluble, non-proteinaceous substance to fulfil the same role – although the nature of this reducing agent is still not fully known. Thus, we have shown that *C. glabrata* has evolved solutions to the problem of iron starvation in the host which frequently differ from those of other pathogenic fungi.

These results allow us to better understand the host-pathogen interaction in *Candida* infections, both from the side of host damage and immune response (Candidalysin) and from the side of pathogen fitness, survival and growth (metal uptake). We will continue to investigate these frontline events at the interface between host and fungus to understand and in the long term disrupt the strategies of Candida species in human pathogenesis.

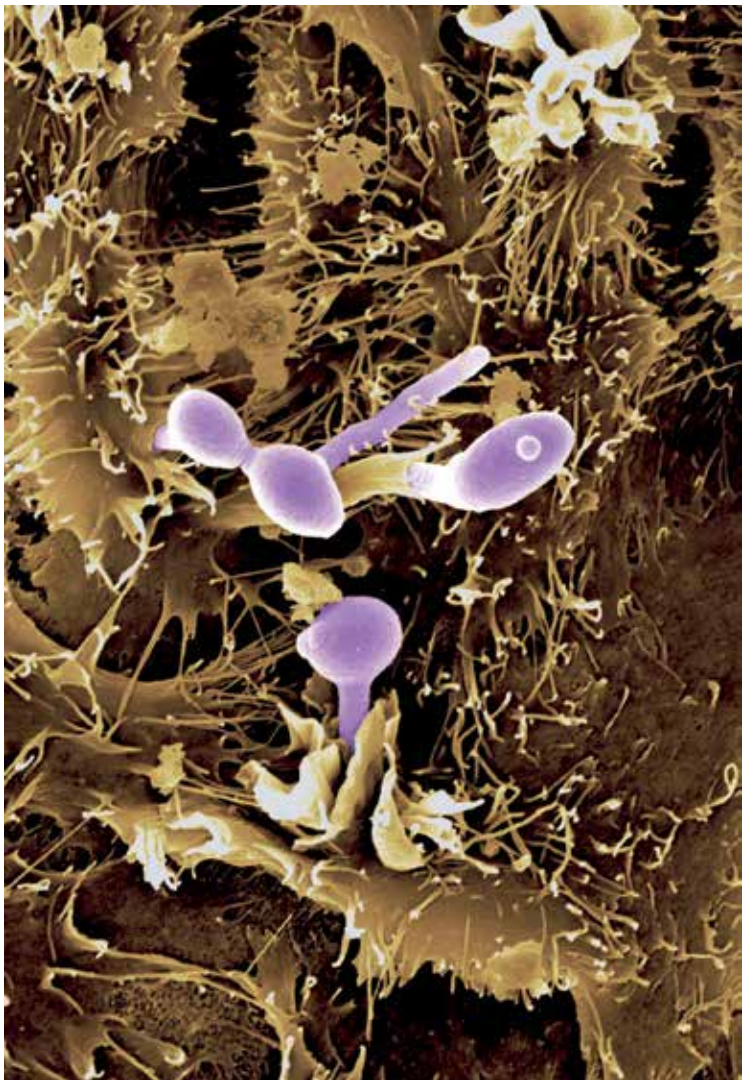


Figure 2: *C. albicans* hyphae (purple) are taken up by oral epithelial cells (induced endocytosis).
Cover photograph - *Science Immunology* 2017 Nov 3;2.

SELECTED COLLABORATIONS

D'Enfert, Christophe
Institut Pasteur, Paris, France

Deckert, Volker
Leibniz Institute of Photonic Technology, Jena, Germany

Ernst, Joachim
Heinrich Heine University Düsseldorf, Germany

Filler, Scott
Harbor UCLA Medical Center, Los Angeles, USA

Gabaldón, Toni
Centre for Genomic Regulation, Barcelona, Spain

Gutsmann, Thomas
Research Center Borstel – Leibniz Lung Center, Borstel, Germany

Kaleta, Christoph
University Hospital Schleswig Holstein, Kiel, Germany

Mansour, Michael
Harvard Medical School, Massachusetts General Hospital, Boston, USA

Morschhäuser, Joachim
Julius Maximilians University Würzburg, Germany

Mosig, Alexander
University Hospital Jena, Germany

Nielsen, Jens
Chalmers University of Technology Gothenborg, Sweden

Pla, Jesús
Universidad Complutense de Madrid, Spain

SELECTED PUBLICATIONS

Verma AH, Richardson JP, Zhou C, Coleman BM, Moyes DL, Ho J, Huppler AR, Ramani K, McGeachy MJ, Mufazalov IA, Waisman A, Kane LP, Biswas PS, Hube B, Naglik JR, Gaffen SL (2017) Oral epithelial cells orchestrate innate type 17 responses to *Candida albicans* through the virulence factor candidalysin. *Sci Immunol* 2, pii: eaam8834.

Gerwien F, Safyan A, Wisgott S, Brunke S, Kasper L, Hube B (2017) The fungal pathogen *Candida glabrata* does not depend on surface ferric reductases for iron acquisition. *Front Microbiol* 8, 1055.

Gerwien F, Safyan A, Wisgott S, Hille F, Kämmer P, Linde J, Brunke S, Kasper L, Hube B (2016) A novel hybrid iron regulation network combines features from pathogenic and nonpathogenic yeasts. *mBio* 7, pii: e01782-16.

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Böttcher B, Pöllath C, Staib P, Hube B, Brunke S (2016) *Candida* species rewired hyphae developmental programs for chlamydospore formation. *Front Microbiol* 7, 1697.

MAJOR THIRD PARTY FUNDING

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project C1 and Z2

DFG: SPP 1580: Intracellular compartments as places of pathogen-host-interactions – Hu 528/17-1

DFG: Identifizierung und Analyse von Chlamydosporen- und Pathogenitäts-assoziierten Genen in *Candida albicans*

BMBF: FunComPath: Fungal Commensal-to-Pathogenicity – WP 2

EU: Marie-Skłodowska-Curie Innovative Training Network Opathy – From Omics to Patient: Improving Diagnostics of Pathogenic Yeasts – ESR9

BMBF: CSCC: Integrated Research and Treatment Centers Center for Sepsis Control and Care – D1.5

DEPARTMENT

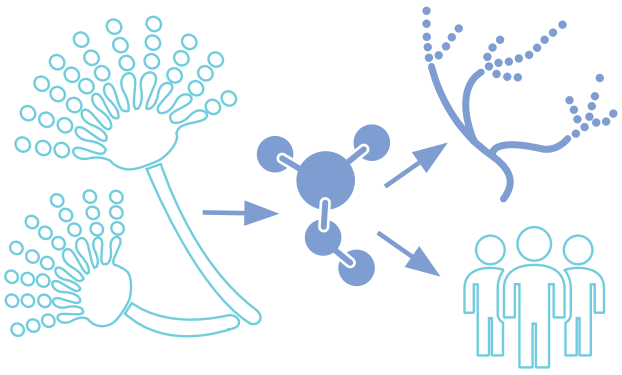
MOLECULAR AND APPLIED MICROBIOLGY

DEPARTMENT
MOLECULAR AND APPLIED MICROBIOLOGY

MOST IMPORTANT RESULTS

Virulence of *Aspergillus fumigatus* and host-pathogen interactions

Research of the group focuses on the identification of virulence determinants of *A. fumigatus* and on the characterization of factors involved in the cross-talk of the pathogen with host immune cells. Within the frame of a joint project with the University of Manchester (UK) a complete gene deletion mutant collection of *A. fumigatus* is currently generated. To date, the project has reached a landmark in having generated a library of nearly 3000 knockouts covering almost a third of the genome. This includes the specific gene knockout collections covering transcription factors, phosphatases, kinases and GPI anchored proteins.



In cooperation with the Research Group Applied Systems Biology we developed novel methods for the bioinformatics-based analysis of life cell imaging. This allowed automated quantification of phagocytosis and thereby identification of fungal molecules inhibiting phagocytosis.

To identify processes that contribute to immune evasion a new protocol to isolate conidia containing phagolysosomes was established and a reference protein map of phagolysosomes was generated. Transmission electron microscopy of conidia-containing macrophages revealed dihydroxynaphthalene melanin dependent structural differences at the phagolysosomal membrane interface. Furthermore, quantitative analysis of the dual proteome of *A. fumigatus* and neutrophils by LC-MS was established. This led to the discovery of novel human proteins involved in the interaction.

Microbial communication and natural products

Natural products (NPs) are important microbial communication molecules. Many of their encoding gene clusters are silent and the mechanisms initiating NP formation are poorly understood. We discovered a specific interaction between the soil bacteria *Streptomyces rapamycinicus* / *S. iranensis* with the filamentous fungus *Aspergillus nidulans* which leads to the activation of the fungal orsellinic acid (ors) gene cluster via manipulation of the fungal chromatin modification. To understand the molecular mechanisms leading to the activation of fungal NP gene clusters we generated and screened a transposon library of *S. iranensis* and established a method for targeted gene deletion. This allowed identify a ferredoxin reductase and an AsnC/Lrp family transcription regulator as being involved in formation of the bacterial signal. Mapping of the chromatin landscape of the fungal-bacterial co-incubation revealed the involvement of a novel transcription factor, BasR, in the targeted expression of the ors gene cluster.

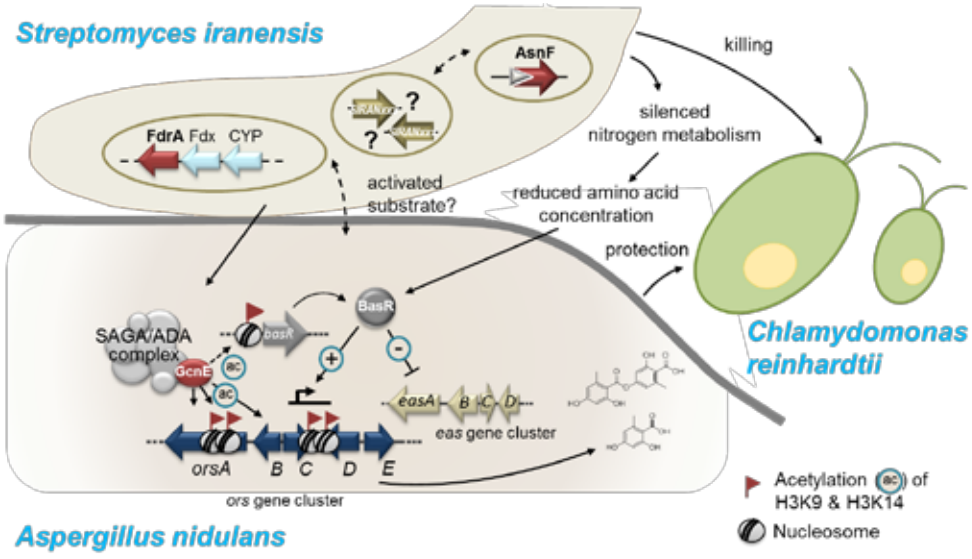


Figure 1: Model of the *S. rapamycinicus/S. iranensis – A. nidulans – Chlamydomonas reinhardtii* interaction. Co-cultivation of bacterium and fungus leads to nitrogen starvation and to reduced amino acid availability in the fungal cell. The lysine-acetyltransferase GcnE specifically acetylates (ac) lysine (K) 9 of histone H3 at the *ors* gene cluster and presumably at the *basR* gene promoter. As a consequence, *basR* is expressed. The deduced transcription factor BasR activates the *ors* gene cluster and suppresses the expression of the eas gene cluster. Culture extracts from *S. iranensis* decolorize/kill *C. reinhardtii* light dependently, but loose activity in co-cultivation of the algae with *A. nidulans* by a yet unknown mechanism.

BasR acts as a novel regulatory node for bacteria-triggered NP production and is functionally conserved in other *Aspergillus* species containing an ors-type gene cluster. We discovered the green algae *Chlamydomonas reinhardtii* to be specifically affected by the co-culture extract thus expanding the model into a tripartite system. *C. reinhardtii* was found to be protected by *A. nidulans* from (light dependent) killing by *S. iranensis*.

Eukaryotic transcription factors

Triazoles are the first-line drugs of systemic antifungal therapy. However, increasing resistance to the azoles is emerging, especially in *A. fumigatus*. Azoles target the cytochrome P450 enzyme sterol-C14α-demethylase Cyp51A. The majority of multi-azole resistant isolates is characterized by the TR34/L98H genetic signature, a combination of a 34 base pair tandem repeat in the cyp51A promoter together with a L98H amino acid substitution within the Cyp51A enzyme. L98H based increase in azole resistance has been associated with limited azole access to the heme containing active site of Cyp51A, however the mechanism of increased cyp51A expression from the TR34 promoter remained enigmatic. The same applies to a recently discovered proline to leucine substitution (P88L) in the *A. fumigatus* CCAAT-binding complex (CBC) subunit HapE that led to increased cyp51A expression. We were able to prove that the transcriptional mechanism of increased cyp51A expression from the TR34 promoter, and consequently azole resistance relies on effective duplication of sterol regulatory elements (SRE) in combination with only partial duplication of the CBC binding site.

Stress- and immunoproteomics

Proteomics, the large-scale study of proteins, has evolved into a powerful approach that enables to quantify thousands of proteins from a microorganism on a global scale. We use both 2D-gel based methods and quantitative LC-MS/MS-based methods for the study of host-fungal pathogen interactions, cellular stress responses and the serological responses of patients against fungal pathogens.

We successfully characterised the serological response of patients with invasive aspergillosis (IA) to *A. fumigatus* protein antigens using serological proteome analysis (SERPA). Altogether, 49 different *A. fumigatus* protein antigens were identified, 18 of which were described as antigenic for the first time. Bioinformatics analyses revealed that the serological response to some *A. fumigatus* antigens was associated with survival of patients (protein CpcB), while others predicted a fatal outcome of the *Aspergillus* infection (protein Shm2). By employing a similar approach, we studied the secreted protein antigens of the pathogenic yeast *Candida albicans*. IgG antibodies to seven extracellular proteins of *C. albicans* may represent predictors of invasive Candida infection. Furthermore, it turned out that protein glycosylation influences significantly the recognition of proteins by antibodies.

We also characterised the pleiotropic effects of commonly used antifungal drugs on *A. fumigatus*. It has been shown that antifungal compounds trigger the intracellular accumulation of reactive oxygen species in pathogenic yeast (ROS). We showed that the mitochondrial respiratory complex I is the main source of ROS, which leads to significant oxidation of the mitochondrial membrane. »

SELECTED COLLABORATIONS

Becker, Katja
Justus Liebig University Giessen, Germany

Böcker, Sebastian
Friedrich Schiller University Jena, Germany

Boland, Wilhelm
Max Planck Institute for Chemical Ecology, Jena, Germany

Braus, Gerhard
Georg August University Göttingen, Germany

Bromley, Mike
University of Manchester, UK

Filler, Scott
University of California, Los Angeles, USA

Fischer, Reinhard
Karlsruhe Institute of Technology, Karlsruhe, Germany

Goldman, Gustavo
University of São Paulo, Brazil

Gunzer, Matthias
University Duisburg-Essen, Germany

Haas, Hubertus
Medical University of Innsbruck, Austria

Kaufmann, Stefan H.E.
Max Planck Institute for Infection Biology, Berlin, Germany

Keller, Nancy
University of Wisconsin Madison, USA

Kothe, Erika
Friedrich Schiller University Jena, Germany

Krappmann, Sven
Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

Lass-Flörl, Cornelia
Medical University of Innsbruck, Austria

Latgé, Jean-Paul
Institut Pasteur, Paris, Frankreich

Leadlay, Peter F.
University of Cambridge, UK

Löffler, Jürgen
University Hospital Würzburg, Germany

Müller, Rolf
Helmholtz Institute for Pharmaceutical Research Saarland, Saarbrücken, Germany

Osherov, Nir
Tel Aviv University, Tel Aviv, Israel

Overmann, Jörg
Leibniz Institute DSMZ German Collection of Microorganisms and Cell Cultures GmbH, Braunschweig, Germany

Popp, Jürgen
Friedrich Schiller University Jena, Germany

Scheffold, Alexander
Charité Universitätsmedizin Berlin, Germany

Speth, Cornelia
Medical University of Innsbruck, Austria

Werz, Oliver
Friedrich Schiller University Jena, Germany

Zychlinsky, Arturo
Max Planck Institute for Infection Biology, Berlin, Germany

SELECTED PUBLICATIONS

Akoumianaki T, Kyrmizi I, Valsecchi I, Gresnigt MS, Samonis G, Drakos E, Boumpas D, Muszkieta L, Zachariou A, Kontoyiannis DP, Chavakis T, Netea MG, van de Veerdonk FL, Brakhage AA, El-Benna J, Beauvais A, Latge JP, Chamilos G (2016) Cell wall melanin regulates fungal pathogenicity via targeting noncanonical autophagy. *Cell Host & Microbe* 19, 79-90.

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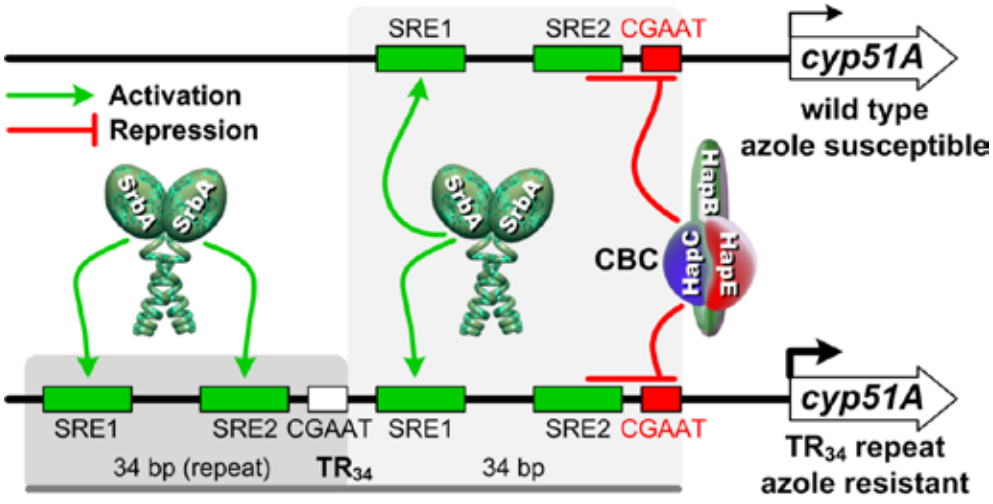

Figure 2: Scheme of the transcriptional mechanisms mediating azole resistance in *A. fumigatus* by the opposing actions of SrbA and the CBC in the promoter region of *cyp51A*.

» OUR DEPARTMENT INVESTIGATES THE INFECTION BIOLOGY OF THE HUMAN-PATHOGENIC FUNGUS *ASPERGILLUS FUMIGATUS* AND NATURAL PRODUCTS FROM FUNGI. OUR AIM IS TO BETTER UNDERSTAND THE HOST-PATHOGEN INTERPLAY AND TO ELUCIDATE THE ROLE OF NATURAL PRODUCTS AS MEDIATORS OF MICROBIAL COMMUNICATION. «

Axel A. Brakhage

Johns A, Scharf DH, Gsaller F, Schmidt H, Heinekamp T, Straßburger M, Oliver JD, Birch M, Beckmann N, Dobb KS, Gilsenan J, Rash B, Bignell E, Brakhage AA*, Bromley MJ* (2017) A nonredundant phosphopantetheinyl transferase, PptA, is a novel antifungal target that directs secondary metabolite, siderophore, and lysine biosynthesis in *Aspergillus fumigatus* and is critical for pathogenicity. *MBio* 8(4). (*corresponding authors)

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MAJOR THIRD PARTY FUNDING

DFG: CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems – Project B2

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project A1 and Z2

DFG: CRC 1278 PolyTarget: Polymer-based nanoparticle libraries for targeted anti-inflammatory strategies – Project B2

DFG: Excellence Graduate School Jena School of Microbial Communication

BMBF: EXASENS – POC-sensor platform for chronic inflammatory respiratory diseases

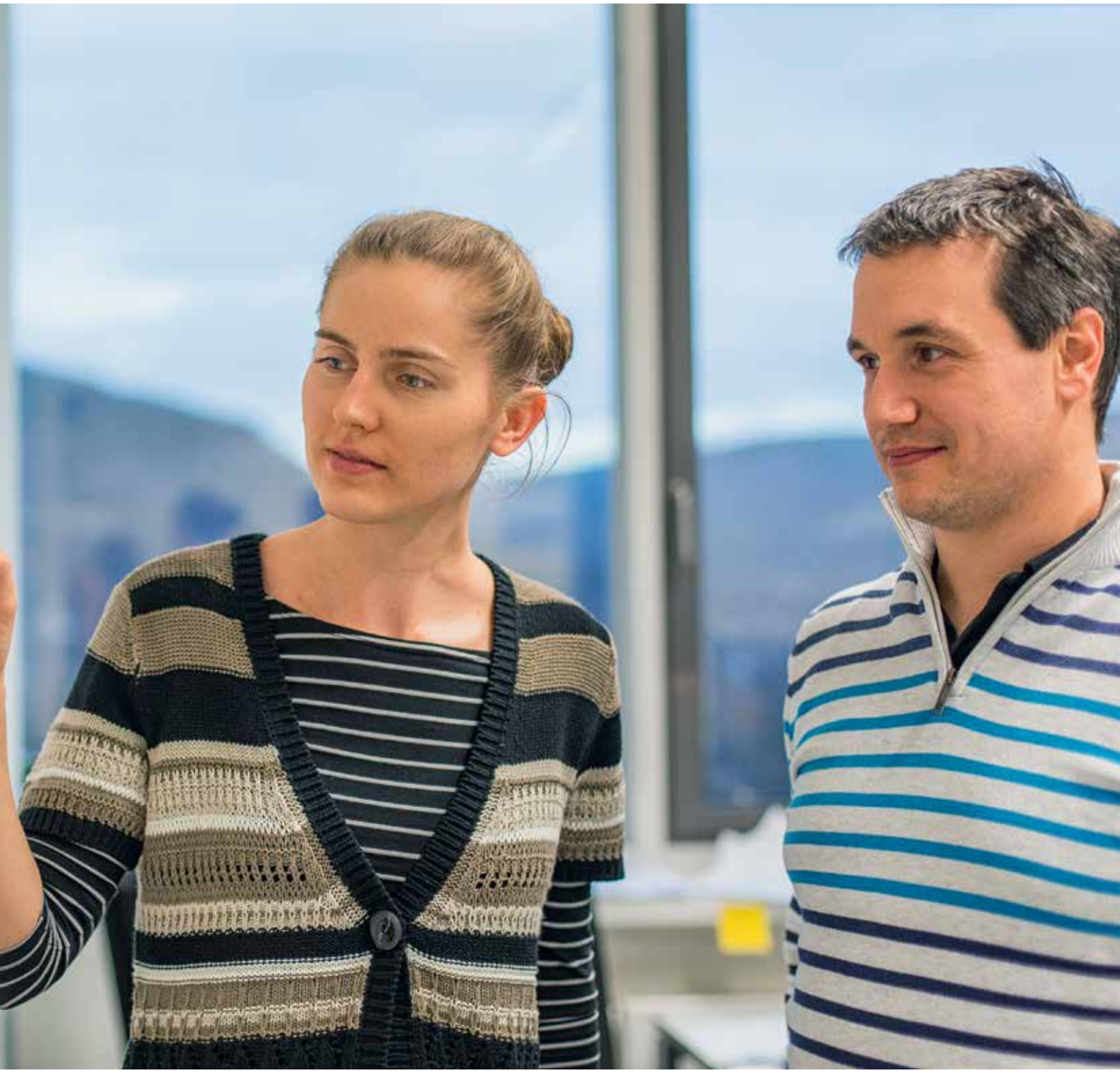
InfectControl 2020: New antiinfection strategies – Science • Society • Economy – Projects FINAR, Transectoral Research Platform, TFP and DIAT

DFG: D-A-CH Lead Agency Action – Novel molecular mechanisms of iron sensing and homeostasis in filamentous fungi

DFG: ANR – Project AfuInf – Proteome and polysaccharidome of *Aspergillus fumigatus* in early stage of infection

RESEARCH GROUP

APPLIED SYSTEMS BIOLOGY



RESEARCH GROUP
APPLIED SYSTEMS BIOLOGY

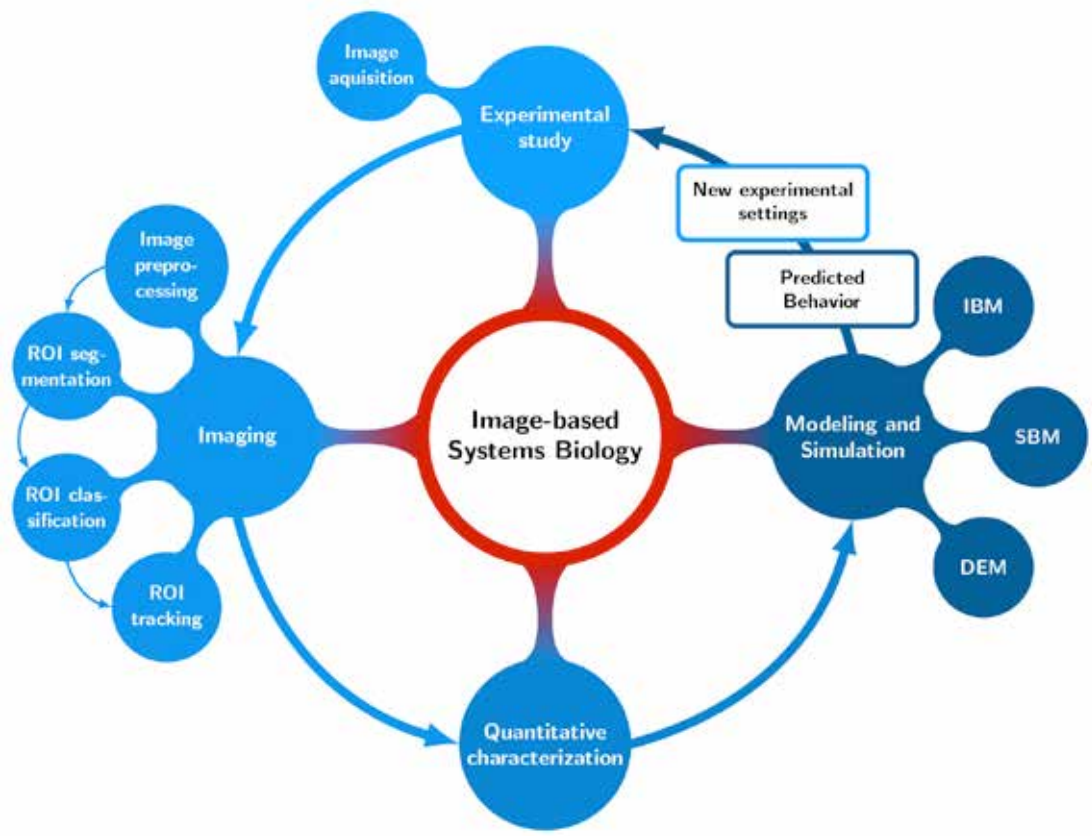
MOST IMPORTANT RESULTS

In the research group Applied Systems Biology, we performed a number of studies in close collaboration with experimental scientists at the Leibniz-HKI and beyond. In this context, algorithms were developed that enable (i) automated image processing, (ii) quantification of biological processes in image data and (ii) computer simulations of virtual infection models.

A previously developed pipeline for the analysis of endpoint imaging experiments on confrontation assays between phagocytes and fungal cells was advanced. This enabled the quantitative investigation of host-pathogen interactions from microscopy data with unlabeled cells. The advantage of performing experiments without labeling cells is two-fold: (i) time-consuming application of fluorescent labels is obsolete and (ii) biological processes are not affected by fluorescent labels. Tracking of unstained cells in live cell imaging videos was extended to the automated analysis of confrontation assays for neutrophils interacting with *Candida glabrata* cells. This enables the investigation of interaction patterns, e.g. to identify whether touching events are prerequisites for phagocytosis events.

Recently, we extended our repertoire of analysis tools to images of various modern imaging modalities. The quantitative analysis of multi-photon microscopy (MPM) data on the interaction of mast cells and dendritic cells in murine tissue *in vivo* revealed the hitherto unknown formation of cell-cell synapses for molecular exchange. Analysis of lightsheet fluorescence microscopy (LSFM) data on whole organs was applied to for the first time quantify the number of kidney glomeruli of mice in health and disease. Furthermore, combination of computed tomography (CT) and positron emission tomography (PET) was applied to quantify *in vivo* bone damage in a murine arthritis model. Taken together, a comprehensive portfolio of various algorithms is available to analyze and quantify biological processes at different spatial and temporal scales.

In cases where systems are highly relevant for infection research but where *in vivo* imaging is technically not possible today, predictive modeling and computer simulation was applied to generate concrete hypotheses that can be tested *in vitro*. For example, to investigate the counterplay of infection and inflammation, we simulated the invasion of the human-pathogenic fungus *Aspergillus fumigatus* in lung alveoli by evolutionary games on graphs. The layered structure of the innate immune system was represented by a sequence of games in the virtual model. We showed that the inflammatory cascade of the immune response was essential for microbial clearance and that the inflammation level correlates with the infection-dose. At low infection-doses, corresponding to daily inhalation of conidia, the resident alveolar macrophages may be sufficient to clear infections, however, at higher infection-doses their primary task shifts towards recruitment of neutrophils to infection sites. »



» THE INVESTIGATION OF DYNAMICAL, FUNCTIONAL AND MORPHOLOGICAL ASPECTS OF INTERACTIONS BETWEEN FUNGI AND THE HUMAN HOST IS PERFORMED BY IMAGE-BASED SYSTEMS BIOLOGY. THIS MODERN APPROACH COMBINES THE AUTOMATED PROCESSING AND QUANTIFICATION OF IMAGES WITH COMPUTER SIMULATIONS OF MATHEMATICAL MODELS. «

Marc Thilo Figge

SELECTED COLLABORATIONS

Dudeck, Anne
Otto von Guericke University Magdeburg, Germany

Gunzer, Matthias
University Duisburg-Essen, Germany

Kamradt, Thomas
University Hospital Jena, Germany

Kurzai, Oliver
Julius Maximilians University Würzburg, Germany

Pohnert, Georg
Friedrich Schiller University Jena, Germany

Schuster, Stefan
Friedrich Schiller University Jena, Germany

SELECTED PUBLICATIONS

Dudeck J*, Medyukhina A*, Froebel J, Svensson C-M, Kotrba J, Gerlach M, Gradtke A-C, Schröder B, Speier S, Figge MT**, Dudeck A** (2017) Mast cells acquire MHCII from dendritic cells during skin inflammation. *J Exp Med* 214, 3791-3811. *authors contributed equally; **corresponding authors, authors contributed equally

Klingberg A, Hasenberg A, Ludwig-Portugall I, Medyukhina A, Männ L, Brenzel A, Engel DR, Figge MT, Kurts C, Gunzer M (2017) Fully automated evaluation of total glomerular number and capillary tuft size in murine nephritic kidneys using lightsheet microscopy. *J Am Soc Nephr* 28, 452-459.

Brandes S, Dietrich S, Hünniger K, Kurzai O, Figge MT (2017) Migration and interaction tracking for quantitative analysis of phagocyte-pathogen confrontation assays. *Medical Image Analysis* 36, 172-183.

Lehnert T, Figge MT (2017) Dimensionality of motion and binding valency govern receptor-ligand kinetics as revealed by agent-based modeling. *Front Immunol* 8, 1692.

Pollmächer J, Timme S, Schuster S, Brakhage AA, Zipfel PF, Figge MT (2016) Deciphering the counterplay of *Aspergillus fumigatus* infection and host inflammation by evolutionary games on graphs. *Sci Rep* 6, 27807.

MAJOR THIRD PARTY FUNDING

DFG: CRC 1278 PolyTarget - Polymer-based nanoparticle libraries for targeted anti-inflammatory strategies – Project Z01

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project B4

Leibniz ScienceCampus InfectoOptics – Project BLOODi

BMBF: CSCC: Integrated Research and Treatment Centers Center for Sepsis Control and Care – Project QUANTIM

Free State of Thuringia (EFRE): DropCode: Microfluidic platform technology for ultra-high throughput screening of novel antimicrobial compounds from microorganisms

Free State of Thuringia (EFRE): AutoScreen: Plattform für die multiparametrische Datenerfassung und -analyse in der tropfenbasierten Mikrofluidik zur Entwicklung von Ultrahochdurchsatz-Screening-Anwendungen für die Biotech-Industrie

RESEARCH GROUP

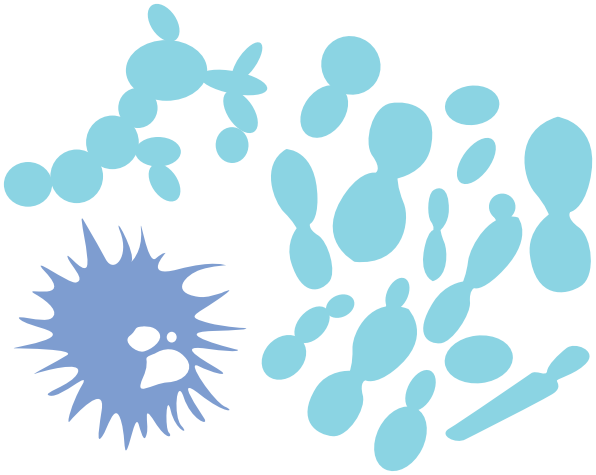
FUNGAL SEPTOMICS

RESEARCH GROUP **FUNGAL SEPTOMICS**

MOST IMPORTANT RESULTS

Virulence of *Candida* spp.

Adaptation to host niches is crucial for pathogenic microbes and virulence of *Candida* spp. is closely related to their ability to respond to environmental changes. We were able to unravel the regulatory pathway central to metabolic adaptation at low CO_2 levels (Pohlers *et al.* 2017, Martin *et al.* 2017). In *Candida albicans*, environmental adaptation frequently triggers filamentation and differential expression of virulence associated genes. In cooperation with the department Microbial Pathogenicity Mechanisms, we contributed to the identification of the first pore-forming toxin in a pathogenic fungus (Moyes *et al.* 2016). Virulence and host adaptation of *C. albicans* have also been studied in a setting of epithelial infection (Böhringer *et al.* 2016)

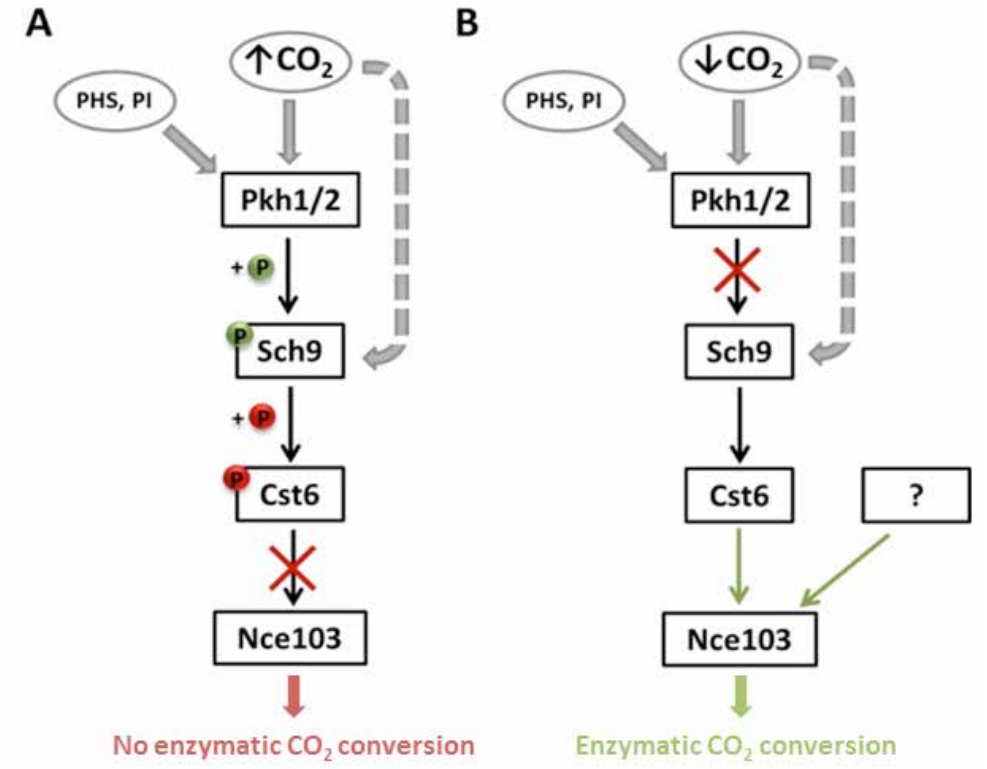


Immune activation in invasive fungal infections (IFI) models

The development of IFI is often facilitated by a disturbed immune response of the host. To investigate the role of various components of the immune system in the activation and maintenance of protective immune responses against fungal pathogens, we established a whole blood infection model and several infection models for primary human immune cells. Using these models, we analysed the role of NK/NKT cells and dendritic cells in fungal infection (Beitzen-Heinecke *et al.* 2016; Czakai *et al.* 2016; Fliesser *et al.* 2017, Hellwig *et al.* 2016; Dix *et al.* 2017; Fischer *et al.* 2017; Ziegler *et al.* 2017). In collaboration with research group Applied Systems Biology a virtual infection model and image analysis algorithms have been developed to quantify host-pathogen interaction dynamics based on live cell imaging data (Brandes *et al.* 2017). In another joint project with the Applied Systems Biology group and the University Hospital Jena, we conduct a pilot study with patient samples to delineate regulatory networks that influence inflammatory processes in IFI and sepsis. Furthermore, we investigate the influence of the quorum-sensing molecule Farnesol produced by *C. albicans* on the immune response of the host (Polke *et al.* 2017a&b).

Genetics of IFI and sepsis

The clinical course of sepsis is influenced by the genetic predisposition of the patient and single nucleotide polymorphisms (SNPs) are suspected to contribute to the development of sepsis. In two genetic studies with sepsis patients, we analysed the influence of SNPs on disease progression and 28-day mortality after



Changes in CO_2 levels trigger filamentation in *C. albicans*. A) At high CO_2 concentrations, spontaneous conversion of CO_2 is sufficient for maintenance of growth. B) At low CO_2 concentrations, the conversion of CO_2 to bicarbonate is strictly dependent on the carboanhydrase Nce103 and the CO_2-dependent activation of Sch9 is mediated by the Pkh1/2 signaling pathway.

sepsis (Scherag *et al.* 2016, Taudien *et al.* 2016). Analyses on the genetics of invasive aspergillosis were successfully continued in cooperation with A. Carvalho, University of Minho, Braga, Portugal (Cunha *et al.* 2017). We are currently pursuing a study with >200 subjects to investigate the influence of SNPs on the immune response against various pathogens that can trigger systemic infections. In this way, we aim to identify potential biomarkers to assess the individual risk of systemic infection in the future.

National Reference Center for Invasive Fungal Infections (NRZMyk)

Clinical oriented research is conducted at the NRZMyk. These projects are described in a separate chapter.

SELECTED COLLABORATIONS

Brabetz, Werner
BioType GmbH, Dresden, Germany

Carvalho, Agostinho
University of Minho, Braga, Portugal

Deising, Holger
Martin Luther University Halle-Wittenberg, Germany

Löffler, Jürgen
University Hospital Würzburg, Germany

Mainz, Jochen
University Hospital Jena, Germany

Riedemann, Niels
InflaRx, Jena, Germany

Romani, Luigina
Università Perugia, Italy

Schmidt, Volker
University Leipzig, Germany

Schumacher, Johannes
University Hospital Bonn, Germany »

» LINKING RESEARCH ON HOST-PATHOGEN INTERACTION TO DIAGNOSIS OF FUNGAL DISEASE WE AIM TO IMPROVE OUR KNOWLEDGE ON INFECTION BIOLOGY AS WELL AS CLINICAL MANAGEMENT. AS NATIONAL REFERENCE CENTER FOR INVASIVE FUNGAL INFECTIONS (NRZMyk) WE SHARE OUR EXPERTISE WITH PARTNERS ALL OVER GERMANY. «

Oliver Kurzai

SELECTED PUBLICATIONS

Cunha C, Gonçalves SM, Duarte-Oliveira C, Leite L, Lagrou K, Marques A, Lupiañez CB, Mesquita I, Gaifem J, Barbosa AM, Pinho Vaz C, Branca R, Campilho F, Freitas F, Ligeiro D, Lass-Flörl C, Löffler J, Jurado M, Saraiva M, Kurzai O, Rodrigues F, Castro AG, Silvestre R, Sainz J, Maertens JA, Torrado E, Jacobsen ID, Lacerda JF, Campos A Jr, Carvalho A (2017) IL-10 overexpression predisposes to invasive aspergillosis by suppressing antifungal immunity. *J Allergy Clin Immunol* 140, 867-870.

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MAJOR THIRD PARTY FUNDING

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project C3

DFG: Polyphasische taxonomische Revision der Mucoraceae

BMG/Robert Koch-Institut: National Reference Center for Invasive Fungal Infections (NRZMyk)

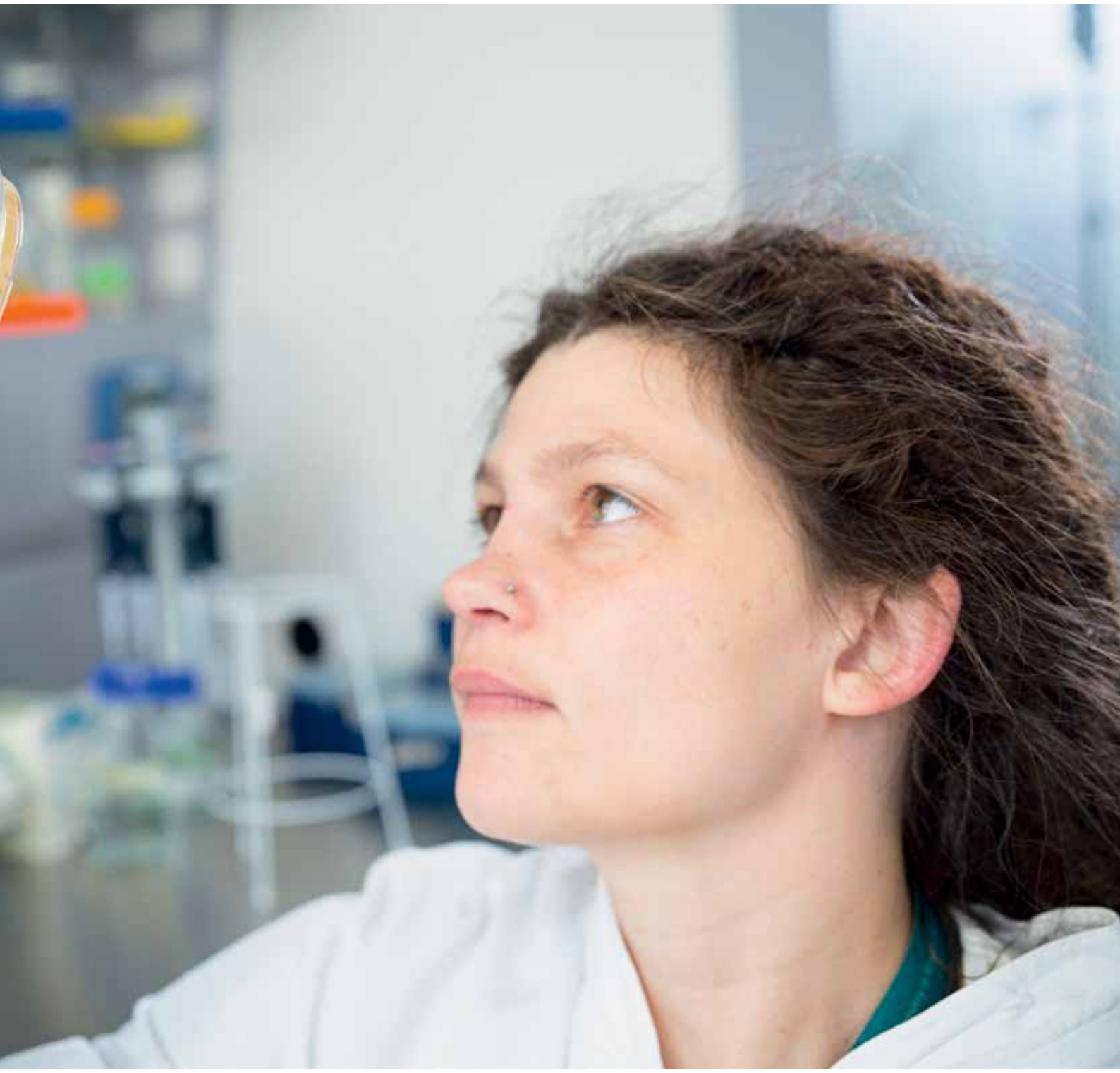
BMBF: InfectControl 2020: New antiinfection strategies – Science • Society • Economy – FINAR

BMBF: CSCC: Integrated Research and Treatment Centers Center for Sepsis Control and Care – QUANTIM

BMBF: InfectControl 2020: New antiinfection strategies – Science • Society • Economy – Transsektorale Forschungsplattform, TV 1, AS2

RESEARCH GROUP

MICROBIAL IMMUNOLOGY



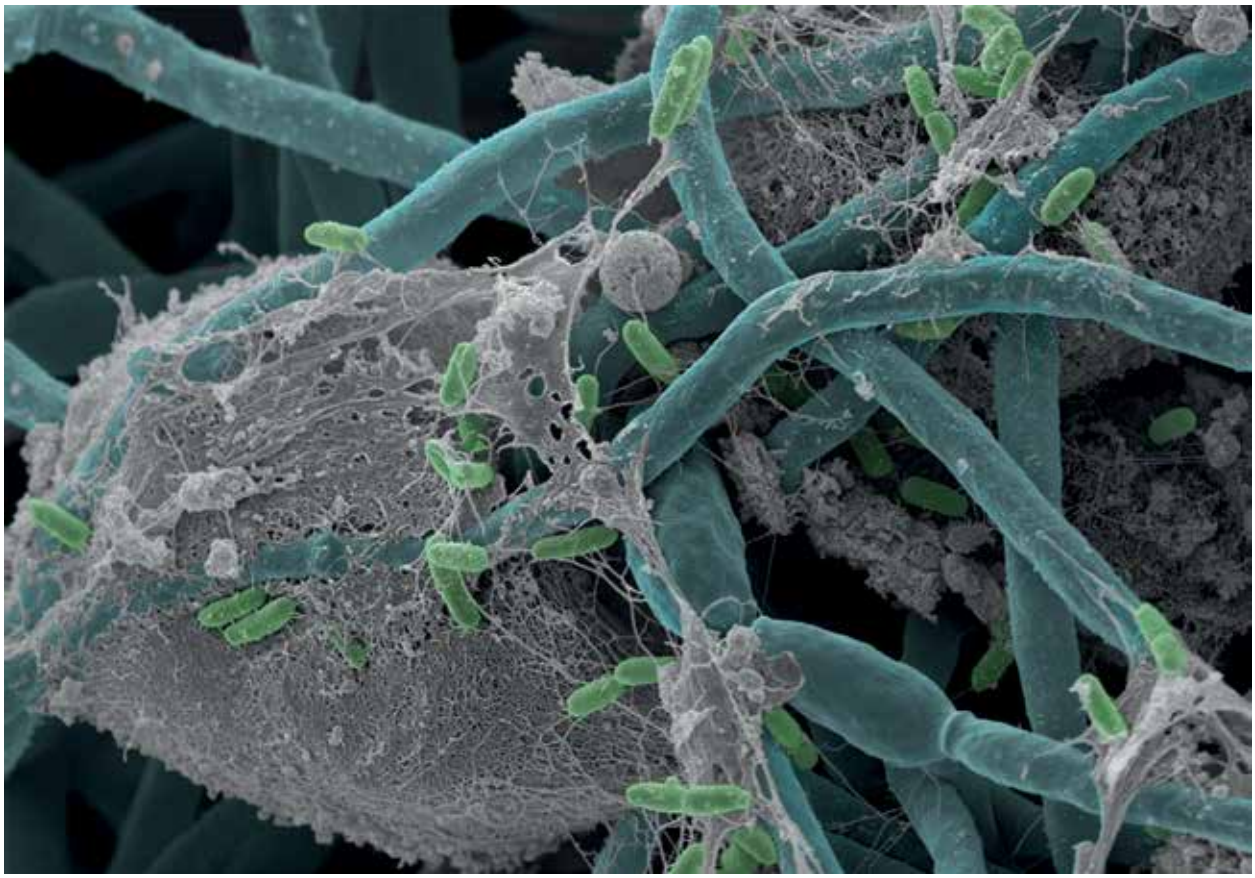
RESEARCH GROUP **MICROBIAL IMMUNOLOGY**

MOST IMPORTANT RESULTS

One research focus of MI is the pathogenesis of disseminated candidiasis. In mice, *C. albicans* infects almost all organs after intravenous application; however, while *C. albicans* is gradually cleared from liver and spleen, infection progresses in the kidneys. To better understand the mechanisms of this organ-specific outcome, we performed gene expression profiling of the fungus and the host tissue during in vivo infection of mice (Hebecker *et al.* 2016). The results indicate a delayed immune response accompanied by unhindered growth of the fungus in the kidneys. In contrast, proinflammatory responses occurred early in the liver and a fungal response suggesting interaction with phagocytes which likely mediates fungal control in the liver. Notably, hypha-associated genes were upregulated in the absence of visible filamentation in the liver, indicating an uncoupling of gene expression and morphology. As morphogenesis is a key virulence attribute of *C. albicans*, we aimed to elucidate the exact role of EED1, a gene required for hyphal maintenance. We discovered that EED1 reduces sensitivity to the filament-inhibitory effect of farnesol, a quorum sensing molecule. In addition, EED1 regulates farnesol production and the hyphal maintenance-defect in the eed1Δ mutant strain is at least partially linked to farnesol (Polke *et al.* 2017). Our findings raise some novel interesting questions concerning farnesol sensing and regulation of production that we will follow up in the future.

The intestinal tract is the main reservoir of *C. albicans* and a source for infections. Using murine models we could show that *C. albicans* behaves as a commensal in this niche and does not trigger inflammatory responses even in a dysbiotic setting. This is likely to be influenced by interactions with bacterial members of the gut microbiota (Niemiec *et al.* 2017). We have found that such interactions influence bacterial virulence *in vitro* and are currently analysing whether this is also the case *in vivo*. Furthermore, alterations of oxygen levels in intestinal tissue, for example during hypoxic shock and reperfusion affect the interaction of *C. albicans* with enterocytes, which might contribute to translocation in specific situations.

Finally, in collaboration with the JMRC we successfully established murine models of pulmonary *Lichtheimia* infection (Schulze *et al.* 2017) that will be used to further investigate pathogenesis of mucormycoses.



Interactions between *C. albicans* and *Proteus mirabilis* on enterocytes visualized by scanning electron microscopy.

SELECTED COLLABORATIONS

Bauer, Michael
University Hospital Jena, Germany

Carvalho, Agostinho
University of Minho, Braga, Portugal

Ebel, Frank
Max von Pettenkofer-Institute for Hygiene and Medical Microbiology of LMU Munich, Germany

Frick, Julia
University Hospital Tübingen, Germany

Gacser, Attila
University of Szeged, Hungary

Haas, Hubertus
Medical University of Innsbruck, Austria

Jungnickel, Berit
Friedrich Schiller University Jena, Germany

Kosan, Christian
Friedrich Schiller University Jena, Germany

Löffler, Bettina
University Hospital Jena, Germany

Mobley, Harry L.T.
University of Michigan, Ann Arbor, USA

Monsen, Tor
Norrlands Universitetssjukhus, Umeå, Sweden

Rosenbauer, Frank
University of Münster, Germany

»

» WE INVESTIGATE THE INTERACTIONS BETWEEN *CANDIDA* AND THE HOST, AIMING AT A BETTER UNDERSTANDING OF THE INTERACTIONS THAT LEAD TO COLONIZATION, PATHOPHYSIOLOGICAL ALTERATIONS AND TO THE DEVELOPMENT OF CLINICAL DISEASE. «

Ilse D. Jacobsen

SELECTED PUBLICATIONS

Hebecker B, Vlaic S, Conrad T, Bauer M, Brunke S, Kapitan M, Linde J, Hube B, Jacobsen ID (2016) Dual-species transcriptional profiling during systemic candidiasis reveals organ-specific host-pathogen interactions. *Sci Rep* 6, 36055.

Polke M, Sprenger M, Scherlach K, Albán-Proaño MC, Martin R, Hertweck C, Hube B, Jacobsen ID (2017) A functional link between hyphal maintenance and quorum sensing in *Candida albicans*. *Mol Microbiol* 103, 595-617.

Polke M, Leonhardt I, Kurzai O, Jacobsen ID (2017) Farnesol signalling in *Candida albicans* – more than just communication. *Crit Rev Microbiol*, 1-14. (Review)

Niemiec MJ, Kapitan M, Polke M, Jacobsen ID (2017) Commensal to pathogen transition of *Candida albicans*. In: Elsevier (ed.) Reference Module in Life Sciences 2017 Elsevier. ISBN: 9780128096338. (Review)

Schulze B, Rambach G, Schwartze VU, Voigt K, Schubert K, Speth C, Jacobsen ID (2017) Ketoacidosis alone does not predispose to mucormycosis by *Lichtheimia* in a murine pulmonary infection model. *Virulence* 8, 1657-1667.

MAJOR THIRD PARTY FUNDING

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project C5

BMBF: InfectoGnostics Research Campus – Diagnostics for Pneumonia in Immunosuppression, subproject New diagnostic methods for fungal infections of the lung

BMBF: CSCC: Integrated Research and Treatment Centers Center for Sepsis Control and Care – Interactions between Candida albicans and bacteria

RESEARCH GROUP

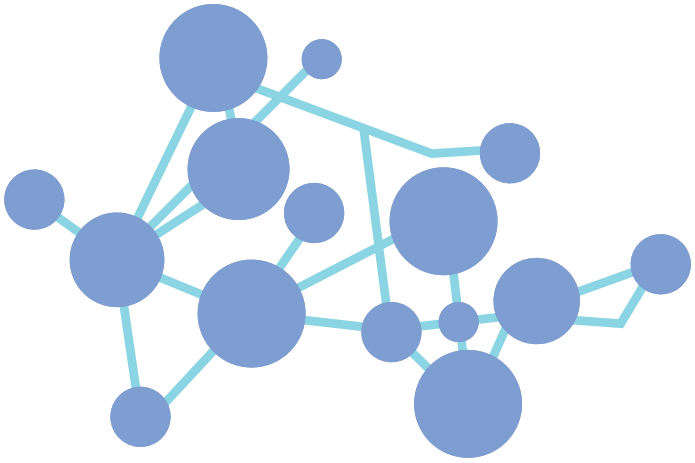
SYSTEMS BIOLOGY AND BIOINFORMATICS

RESEARCH GROUP
SYSTEMS BIOLOGY AND BIOINFORMATICS

MOST IMPORTANT RESULTS

In collaboration with experimental groups, various genome and (dual) RNA-Seq data were analysed in particular of the fungal genera *Aspergillus*, *Candida*, *Serpula* and *Verticillium* as well as Streptomycetes, Enterococci on the pathogen site and murine organs (kidney, liver etc) or the plant *Arabidopsis thaliana* at the host site.

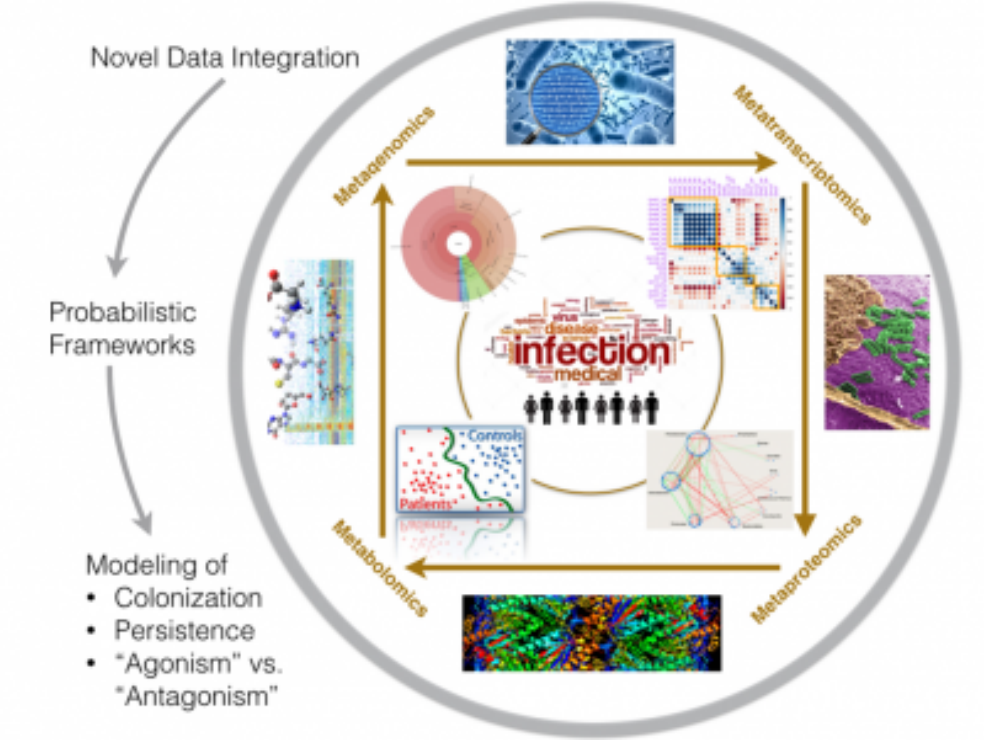
By applying next-generation sequencing of small RNAs, we discovered specific and novel microRNAs that regulate the response to fungal infection with *C. albicans* and *A. fumigatus* in human dendritic cells. Our results indicate that these micSroRNAs fine-tune the expression of immune-related target genes during fungal infection.



By comparative genomics and in collaboration with experimental groups, we characterized the secondary metabolism of fungi in its integrity, developing systems biology approaches to describe secondary metabolite gene clusters, as well as their regulation and evolution. We investigated entire repertoires of transcription factors (TFomes) in more than 200 fungal species. In particular, we revealed high biological diversity and specific adaptations in the fungal genus *Aspergillus*.

We integrated our software CASSIS (Cluster Assignment by Islands of Sites), a method for Secondary Metabolite (SM) Synthesis cluster prediction in eukaryotic genomes, and SMIPS (SM by InterProScan), in the tool antiSMASH for genome-wide detection of SM key enzymes.

We developed and published the software tool ModuleDiscoverer for the identification of regulatory modules from protein-protein interaction networks and gene expression data. Using this tool, we identified the regulatory module underlying a rodent model of non-alcoholic steatohepatitis (NASH), a severe form of non-alcoholic fatty liver disease. Furthermore, we applied this novel tool to study the transcriptome, proteome and secretome from the human pathogenic fungus *Aspergillus fumigatus* challenged with the antifungal drug caspofungin. The additional structural information of the network of interacting modules allowed for topological analyses as well as the investigation of drug-caused side effects like the involvement of the non-differentially expressed or regulated polyubiquitin that it plays a key role in the *A. fumigatus* response to caspofungin.



Develop models that describe the interplay of hosts, commensal microbes and diseases

We analysed the metagenome to understand the role of microbial communities in antibiotic resistance development and dissemination, progression of disease and the development of therapeutic interventions.

We published the second release of our database NutriChem that links plant-based foods with their small molecule components and human health effect.

We studied the differential biphasic transcriptional murine host response during severe influenza by modelling of gene regulatory network. The two key inflammatory cytokines, interferon gamma and interleukin 6, were found to contribute to the key mechanisms contributing to co-pathogenesis of two of quasispecies of influenza A virus. »

SELECTED COLLABORATIONS

Baker, David
The University of Hong Kong, China

El-Nezami, Hani
University of Eastern Finland, Kuopio, Finland

Henkel, Sebastian
BioControl Jena GmbH, Jena, Germany

Jia, Weiping
Shanghai Jiao Tong University, Shanghai, China

Löffler, Jürgen
University Hospital Würzburg, Germany

Lohinai, Zoltan
National Koranyi Institute of Pulmonology, Budapest, Hungary

Overmann, Jorg
Leibniz Institute DSMZ German Collection of Microorganisms and Cell Cultures GmbH, Braunschweig, Germany

Polańska, Joanna
Silesian University of Technology Gliwice, Poland

Singer, Mervyn
University College London, UK

Sommer, Morten
Technical University of Denmark, Copenhagen, Denmark

Yan, Aimin
The University of Hong Kong, China

SELECTED PUBLICATIONS

Li J, Ying Ju Sung C, Lee N, Ni Y, Pihlajamäki J, Panagiotou G, El-Nezami H (2016). Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. *Proc Natl Acad Sci USA* 113, E1306-15.

Blin K, Wolf T, Chevrette M, Lu X, Schwalen C, Kautsar S, Suarez Duran, H, de los Santos E, Kim HU, Nave M, Dickschat J, Mitchell D, Shelest E, Breitling R, Takano E, Lee SY, Weber T, Medema M (2017) antiSMASH 4.0 – Improvements in chemistry prediction and gene cluster boundary identification. *Nucleic Acids Res* 45(W1), W36-W41.

Zheng T, Ni Y, Li J, Chow BKC, Panagiotou G (2017) Designing dietary recommendations using system level interactomics analysis and network-based inference. *Front Physiol* 8, 753.

MAJOR THIRD PARTY FUNDING

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Projects B3, B5 and INF

DFG: CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems – Project INF

Free State of Thuringia (ESF): Researcher Group PiDOMICS – Pilzinfektionen: neue Verfahren zur Diagnose und zum Therapiemonitoring mit Hilfe von OMICS-Technologien und Bioinformatik

» THE MAIN OBJECTIVE OF THE RESEARCH GROUP IS TO DISCOVER MOLECULAR MECHANISMS USING AN ITERATIVE CYCLE STARTING WITH THE INTEGRATED COMPUTATIONAL ANALYSIS OF EXPERIMENTAL DATA, INCLUDING OMICS AND META-OMICS DATAAND ENDS WITH EXPERIMENTAL VALIDATION. «

Gianni Panagiotou

INDEPENDENT JUNIOR RESEARCH GROUP

BIOBRICKS OF MICROBIAL NATURAL PRODUCT SYNTHESES


Thermo

INDEPENDENT JUNIOR RESEARCH GROUP
BIOBRICKS OF MICROBIAL NATURAL PRODUCT SYNTHESES

MOST IMPORTANT RESULTS

Setting up a toolbox for studying natural products from eukaryotes

Fungi are considered an inestimable source of natural products (NPs). Many of these active compounds have been highly beneficial for humankind serving as therapeutics. Because the majority of fungal species are recalcitrant to standard lab conditions and genetic manipulation, the discovery of novel NPs is still limited. Alternately, the discovery process can be improved by heterologously expressing unknown metabolic pathways in model organisms.

We recently developed a new method based on the expression of polycistronic genes in eukaryotes using the 2A peptide sequences from Picornaviruses. Picornaviruses have a positive single stranded RNA genome containing polycistrons. Picornaviruses' polycistrons express genes joined by self-splicing peptide sequences, such as the 2A, that are recognized by eukaryotic ribosomes. The cleavage of the nascent self-splicing peptides permits a continuous translation.

In the last year this tool was implemented at different levels:

- Isolation and cloning of the genes of interested was simplified developing a very efficient plasmid assembly line.
- We designed a screening system based on a split-YFP marker gene, which releases fluorescence only when is reassembled in the nucleus, reducing the possibility of selecting false positives to zero.
- The 2A tags were manipulated in order to be removed in vivo after protein translation.

This methodology is currently used for rewiring metabolic pathways, for producing valuable compounds in fermenting conditions, and for the discovering of computationally identified biosynthetic gene clusters.

In vitro production of active molecules

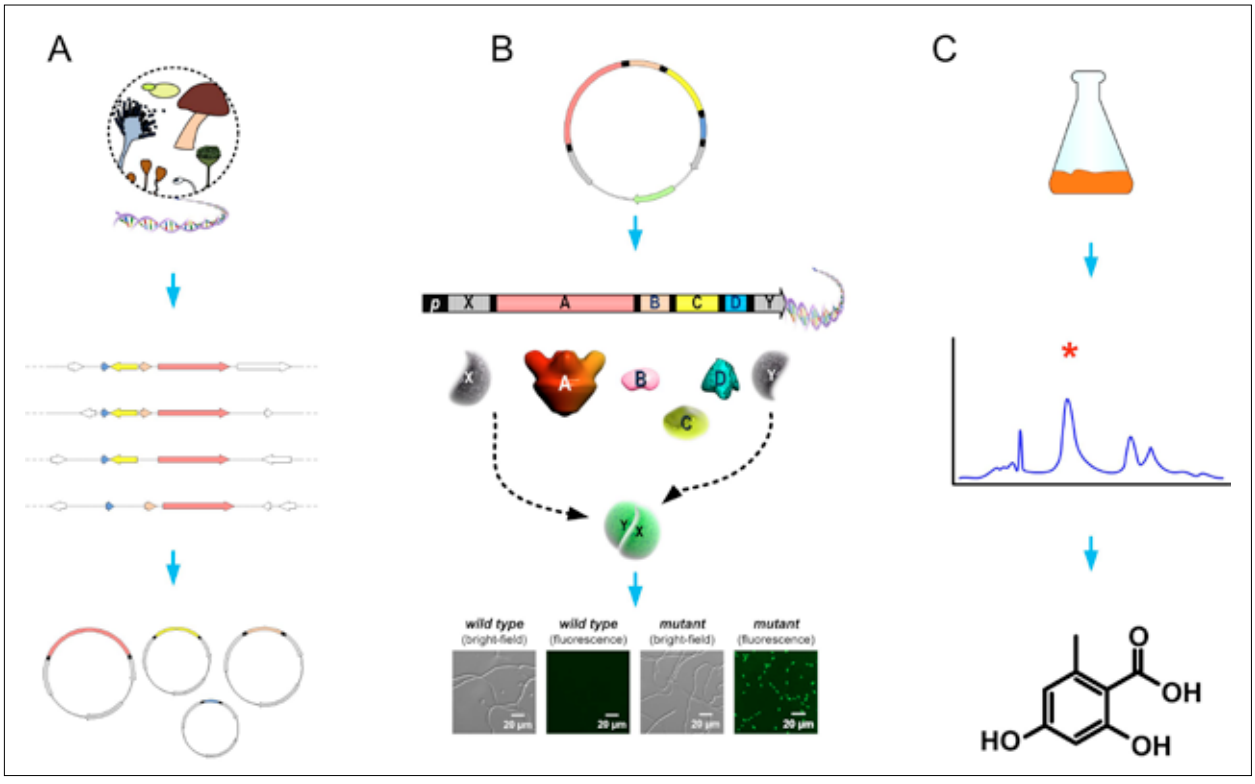
Fungal polyketide synthases predominantly use malonyl-CoA extender units to build carbon skeletons. The production of polyketides *in vitro* is still limited by the availability of polyketide's precursors, such as malonyl- and acetyl-CoA. The MatB from *Rhizobium* sp. is a malonyl-CoA synthases that catalyses malonyl-CoA formation by ligation of malonate salt and CoA, while MatA catalyses the formation of acetyl-CoA by decarboxylating malonyl-CoA. MatB and MatA were both purified and immobilized on Ni-NTA magnetic beads. In cooperation with partners from the Leibniz Research Clusters (LRC) we developed a microfluidic system able to efficiently produce malonyl-CoA and acetyl-CoA in a continuous flow. Additionally, using magnetic force, the system permitted the recycling of the enzymes and their re-utilization.

Regulation of DHN-melanin in *Aspergillus fumigatus*

Mitogen activated protein kinases (MAPKs) play a significant in *Aspergillus fumigatus* infection. *A. fumigatus* produces DHN-melanin, a secondary metabolite associated to the fungal cell wall, important to protect fungal cells from exogenous hazards. We have elucidated the upstream regulators of the pheromone MAPK pathway and its involvement in DHN-melanin production. »

» THE BMN GROUPS MISSION IS THE DISCOVERY OF NOVEL ACTIVE COMPOUNDS AND THE DEVELOPMENT OF NEW STRATEGIES FOR THEIR PRODUCTION. MAJOR FOCUSES ARE: CREATING NEW TOOLS FOR COMPOUND DISCOVERY; ISOLATION OF ENZYMES USABLE FOR CELL-FREE BIOSYNTHESIS; UNDERSTANDING NATURAL PRODUCTS REGULATION IN FUNGI. «

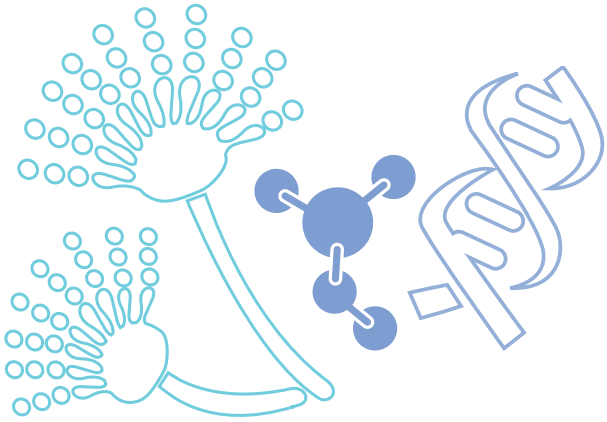
Vito Valiante



A Biosynthetic gene clusters are computationally identified from genome databases. Selected genes are individually cloned in an appropriate vector.

B Using the plasmid assembly line, genes are fused as a polycistron exploiting the 2A peptide sequences (reported in black). The polycistron containing plasmid is used to transform the appropriate model fungus. The split-YFP marker, included in the polycistron, is used for the selection of the obtained mutants by fluorescence microscopy.

C The transformed fungus is cultivated and novel metabolites identified by chromatography.



SELECTED COLLABORATIONS

Bromley, Mike
University of Manchester, UK

Cui, Jiaxi
Leibniz Institute for New Materials, Saarbrücken, Germany

Freier, Erik
Leibniz Institute for Analytical Sciences, Dortmund, Germany

Goldman, Gustavo
Universidade de São Paulo, Brazil

Thiele, Julian
Leibniz Institute of Polymer Research, Dresden, Germany

SELECTED PUBLICATIONS

Manfiolli AO, de Castro PA, Dos Reis TF, Dolan S, Doyle S, Jones G, Riaño Pachón DM, Ulaş M, Noble LM, Mattern DJ, Brakhage AA, Valiante V, Silva-Rocha R, Bayram O, Goldman GH (2017) *Aspergillus fumigatus* protein phosphatase PpzA is involved in iron assimilation, secondary metabolite production, and virulence. *Cell Microbiol* 19, e12770.

Mattern DJ, Valiante V, Horn F, Petzke L, Brakhage AA (2017) Rewiring of the austinoid biosynthetic pathway in filamentous fungi. *ACS Chem Biol* 12, 2927-2933.

Valiante V (2017) The cell wall integrity signaling pathway and its involvement in secondary metabolite production. *Journal of Fungi* 3, 68.

Valiante V, Mattern DJ, Schüffler A, Horn F, Walther G, Scherlach K, Petzke L, Dickhaut J, Guthke R, Hertweck C, Nett M, Thines E, Brakhage AA (2017) Discovery of an extended austinoid biosynthetic pathway in *Aspergillus calidoustus*. *ACS Chem Biol* 12, 1227-1234.

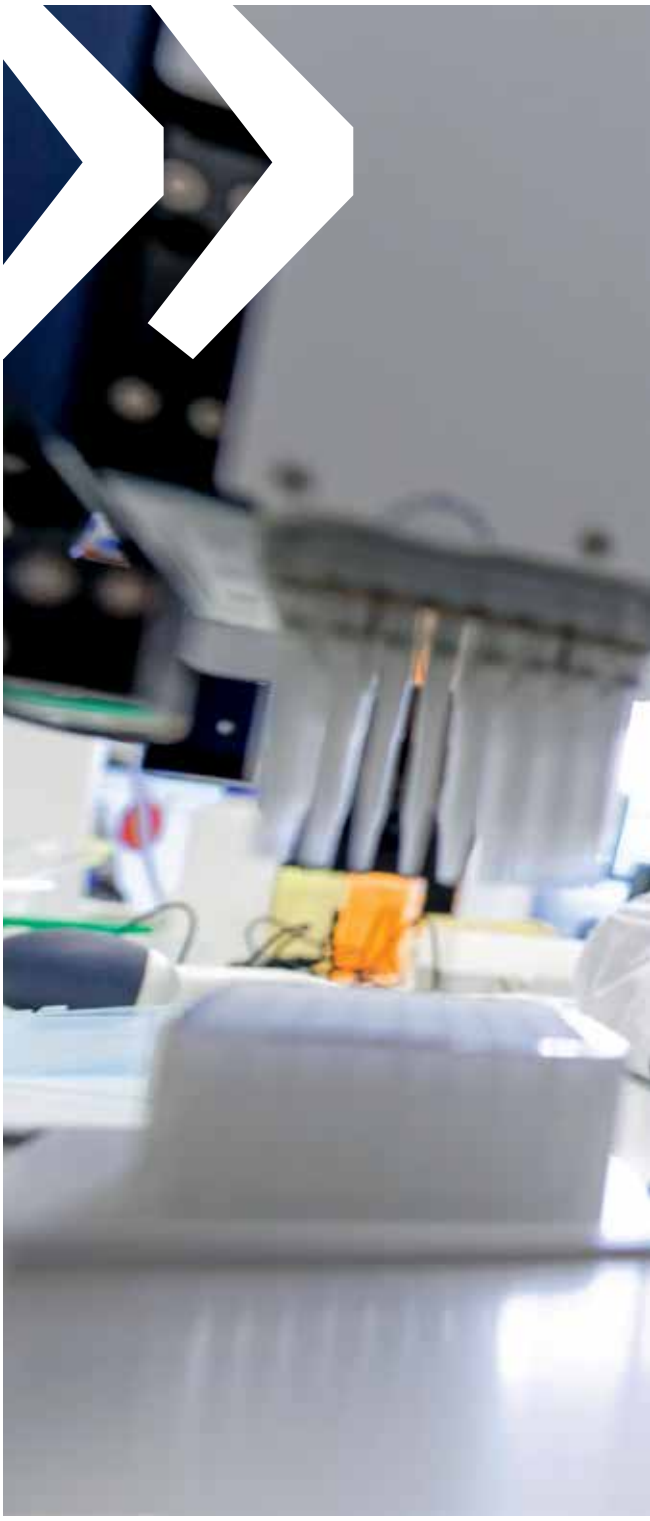
Weber J, Valiante V, Nødvig CS, Mattern DJ, Slotkowski RA, Mortensen UH, Brakhage AA (2017) Functional reconstitution of a fungal natural product gene cluster by advanced genome editing. *ACS Synth Biol* 6, 62-68.

MAJOR THIRD PARTY FUNDING

BMBF: LRC: Leibniz Research Cluster Bio/synthetic multifunctional micro production units – novel ways of compound development

INDEPENDENT JUNIOR RESEARCH GROUP

BIOSYNTHETIC DESIGN OF NATURAL PRODUCTS



INDEPENDENT JUNIOR RESEARCH GROUP
BIOSYNTHETIC DESIGN OF NATURAL PRODUCTS

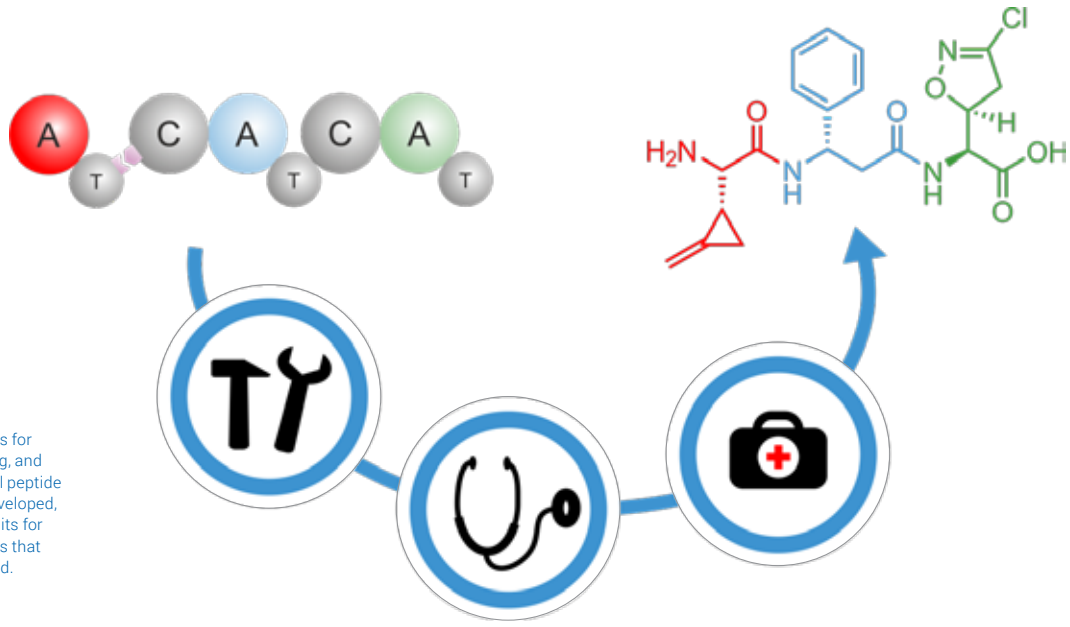
MOST IMPORTANT RESULTS

We approach the design of nonribosomal peptide synthetases by mimicking the natural evolution of these enzymes. In directed evolution experiments, mutations are sprinkled over the enzymes and improved variants are retrieved from large libraries of mutants. Alternatively, we swap parts of the synthetases similar to natural recombination events. On the way towards a reliable pipeline for the redesign of nonribosomal peptide synthetases (NRPSs), we have to overcome several obstacles. First, the substrate specificity of nonribosomal adenylation domains is too difficult to assess for effective mutant screening. Second, the library sizes obtained for the directed evolution of NRPSs are often too small and relevant phenotypes fail to be screened. Third, the structural biology of large NRPSs with many concatenated domains is highly complex. We have made progress on these issues since we started setting up our labs at Leibniz-HKI in September 2016.

We are evaluating a novel screening format for the adenylation activity of the specificity determining gate-keeper domains of NRPSs. This LC-MS/MS assay should be able to retrieve meaningful kinetic parameters from a parallel reaction of dozens of amino acid substrates with one adenylation domain. Preliminary data indicate that hydroxamates formed after quenching activated amino acids with hydroxylamine can indeed be detected at sufficient sensitivity. Hydroxamate standards of more than 20 amino acids have been prepared to calibrate the assay. To demonstrate the potential of the assay, we want to apply it on cryptic adenylation domains cloned from the monocellular algae *Cyanophora paradoxa* in collaboration with the group of Prof. Severin Sasso (FSU Jena).

A high-throughput screen for antibiotic activity would enable us to perform directed evolution experiments on NRPSs while screening for a phenotype directly relevant for medical applications. In order to establish such a screen in microfluidics format, we have tested the action of the nonribosomal peptide gramicidin S in microdroplets together with Lisa Mahler and Dr. Martin Roth. The inhibitory effect of a natural gramicidin S producer on a labeled reporter strain of *Bacillus subtilis* was clearly detected in droplets, auguring well for the application of a microfluidics-based sorting strategy for NRPS evolution. *E. coli* as a genetically tractable, heterologous host for gramicidin S production has yielded extracellular concentrations only 10-fold below the minimum inhibitory concentration of the reporter strain.

Shuffling of small, specificity determining genetic parts of NRPSs (subdomains) made by gene synthesis has been proposed for the generation of NRPS diversity. We have synthesized a mechanism-based inhibitor for a kinetically impaired, subdomain-swapped adenylation domain. We are currently attempting co-crystallization of enzyme and inhibitor in order to learn about the adverse effects of subdomain swapping to later refine the swapping strategy.



When efficient pipelines for engineering, diagnosing, and repairing nonribosomal peptide synthetases can be developed, creativity knows no limits for the diversity of peptides that could be biosynthesized.

SELECTED COLLABORATIONS

Hilvert, Donald
ETH Zurich, Switzerland

O'Connor, Sarah
John Innes Centre, Norwich, UK

Sasso, Severin
Friedrich Schiller University Jena, Germany

SELECTED PUBLICATIONS

Kries H, Kellner F, Kamileen M, O'Connor SE (2016) Inverted stereocontrol of iridoid synthase in snapdragon. *J Biol Chem* 292, 14659-14667.

Niquille D, Hansen D, Mori T, Fercher D, Kries H, Hilvert D (2017) Nonribosomal biosynthesis of backbone-modified peptides. *Nat Chem*, 10, 282-287.

MAJOR THIRD PARTY FUNDING

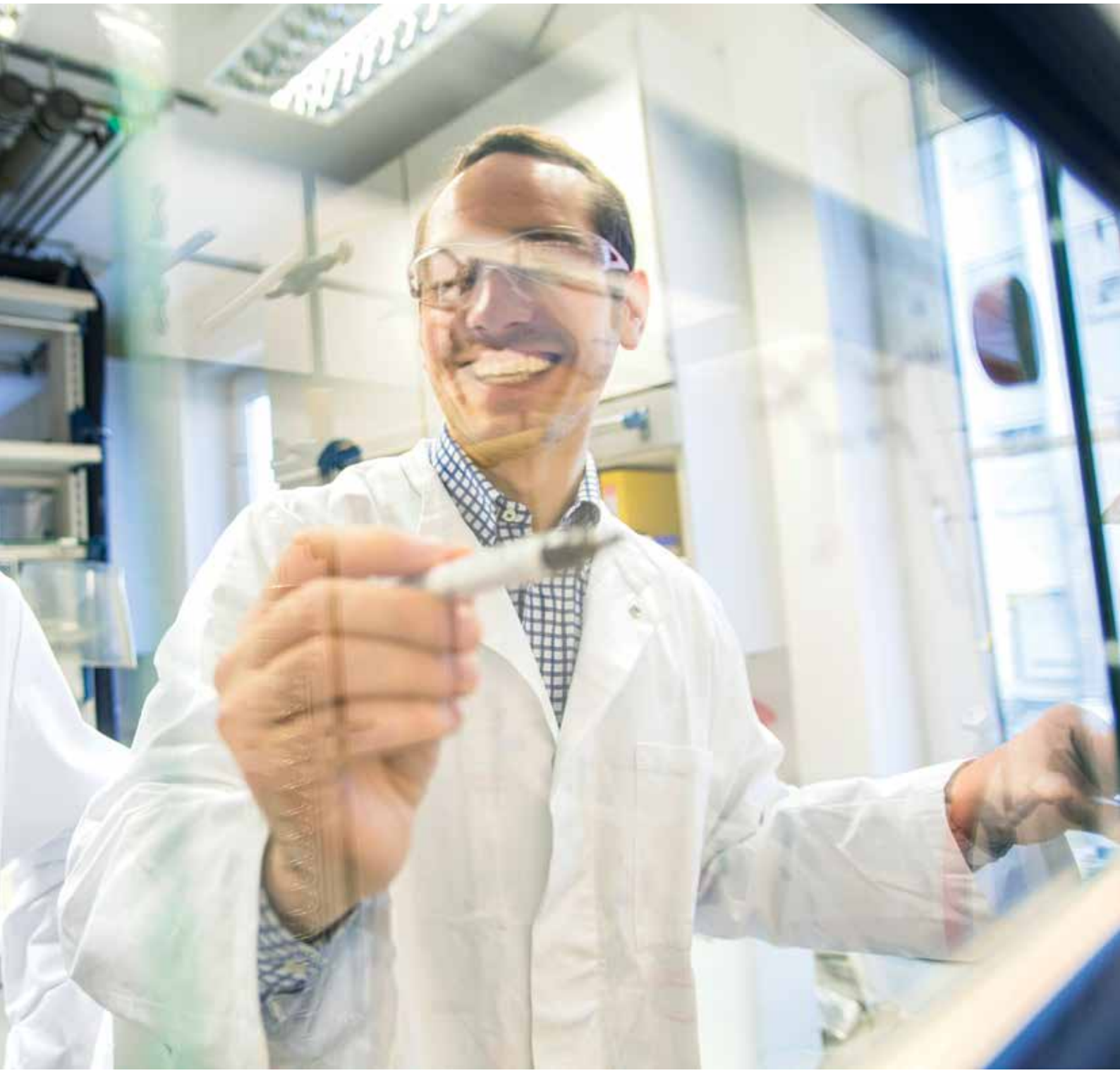
Daimler und Benz Stiftung: A pipeline for biosynthetic engineering of antibiotic peptides

» NATURAL PRODUCTS ENGENDER DIVERSE BIOACTIVITIES, YET WE HOPE TO FURTHER IMPROVE AND VALORIZE THEM BY TINKERING WITH THEIR BIOSYNTHETIC PATHWAYS. WE AIM TO STREAMLINE THE BIOSYNTHETIC DESIGN OF NONRIBOSOMAL PEPTIDE SYNTHETASES TO A POINT WHERE CUSTOMIZED PEPTIDES CAN BE BIOSYNTHESIZED ON DEMAND. «

Hajo Kries

INDEPENDENT JUNIOR RESEARCH GROUP

CHEMISTRY OF MICROBIAL COMMUNICATION



INDEPENDENT JUNIOR RESEARCH GROUP
CHEMISTRY OF MICROBIAL COMMUNICATION

MOST IMPORTANT RESULTS

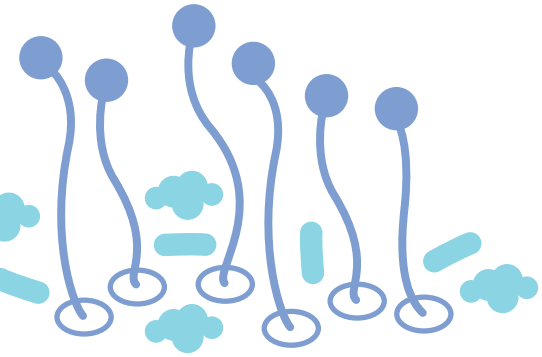
In the advent of multidrug-resistant infectious diseases, the identification of new anti-infectives, in particular antimicrobial natural products, is of utmost urgency. Our group particularly focuses on ecological scenarios, in which bacteria defend themselves against predators by the secretion of such bioactive natural products. As model predator, we use the social amoeba *Dictyostelium discoideum*, which can devour up to 300 bacteria per hour and thus represents one of the most important predators to soil bacteria.
We identified novel natural products that enable *Pseudomonas fluorescens* to defend itself against amoebal predators. *P. fluorescens* HKI0770 produces a novel class of bacterial alkaloids, the pyreudiones, which display potent amoebicidal activity (Klapper *et al.* 2016). We determined their structures based on different spectroscopic and spectrometric techniques as well through a total synthesis. Furthermore, we elucidated the biosynthesis of these alkaloids. The pyreudiones are biosynthesized by a novel type of a minimalistic nonribosomal peptide synthetase, which effectively condenses L-proline and a 3-oxo-fatty acid moiety. In collaboration with the group of Prof. O. Werz (FSU Jena) we determined the mode of action of the pyreudiones.

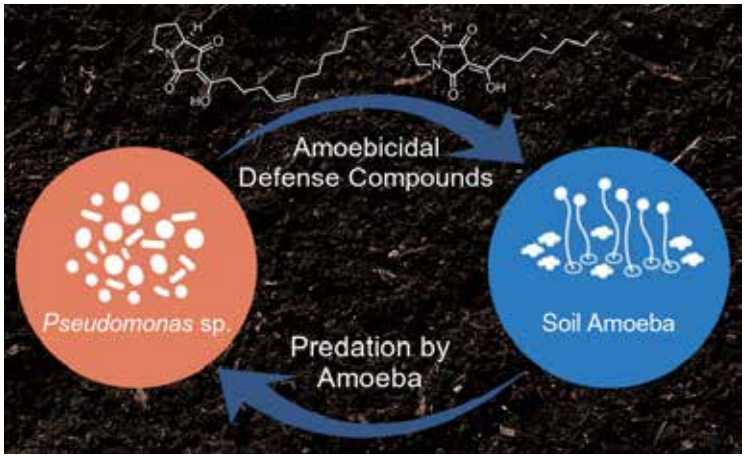
In addition to the pyreudiones, we could show that the cyclic lipopeptide anikasin extends the amoebicidal spectrum of *P. fluorescens* HKI0770 (Goetze et al. ACS Chem Biol 2017). We could determine the structure of anikasin via X-ray crystal structure analysis. Detailed analyses of *P. fluorescens* mutants impaired in the synthesis of the pyreudiones, anikasin, or both allowed us to map the detailed antiprotozoal spectrum of the respective compounds.

Investigations of amoeba-associated bacteria led to the discovery of another novel Pseudomonas-derived cyclic lipopeptide, which is co-secreted with the known polyketide mupirocin. Both natural products are quorum-sensing regulated and display synergistic activity against the human pathogen methicillin-resistant *Staphylococcus aureus*.

» THE MISSION OF THIS RESEARCH GROUP IS TO IDENTIFY NOVEL NATURAL PRODUCTS FROM INTERACTING MICROBES, IN PARTICULAR BACTERIA AND THEIR PREDATORS. WE ELUCIDATE THE STRUCTURE OF THE METABOLITES AND IDENTIFY THEIR BIOSYNTHESES, BIOLOGICAL ACTIVITY, AND ECOLOGICAL FUNCTION. «

Pierre Stallforth





Soil bacteria are constantly threatened by various predators. Some bacteria can defend themselves via the secretion of natural products with anti-predator activity.

Our group also investigates natural products derived from social amoebae. We provided a total synthesis of the signal molecule glorin, which coordinates multicellular aggregation of the amoeba *Polysphondylium pallidum* (Barnett *et al.* 2017). This synthetic route enabled us to perform a structure-activity relationship study of glorin for the construcion of a chemical probe to identify the so far unknown glorin receptor as well as enzymes that degrade glorin (in collaboration with Prof. T. Winckler, FSU Jena). Furthermore, we investigate the role of polyketide synthases in social amoebae. We established effective molecular biology tools to obtain gene KO mutants in *D. discoideum* and to heterologously express genes in this organism. Efforts to implement the CRISPR-Cas9 system in this social amoeba are currently ongoing.

SELECTED COLLABORATIONS

Hoffmeister, Dirk
Friedrich Schiller University Jena, Germany

Kovács, Ákos
Friedrich Schiller University Jena, Germany

Queller, David
Washington University in St. Louis, USA

Strassmann, Joan
Washington University in St. Louis, USA

Werz, Oliver
Friedrich Schiller University Jena, Germany

SELECTED PUBLICATIONS

Klapper M, Götze S, Barnett R, Willing K, Stallforth P (2016) Bacterial alkaloids prevent amoebal predation. *Angew Chem Int Ed* 55, 8944-8947.

Götze S, Herbst-Irmer R, Klapper M, Görls H, Schneider KRA, Barnett R, Burks T, Neu U, Stallforth P (2017) Structure, biosynthesis, and biological activity of the cyclic lipopeptide anikasin. *ACS Chem Biol* 12, 2498-2502.

Gallegos-Monterrosa R, Kankel S, Götze S, Barnett R, Stallforth P, Kovács AT (2017) *Lysinibacillus fusiformis* M5 induces increased complexity in *Bacillus subtilis* 168 colony biofilms via hypoxanthine. *J Bacteriol* 199, e00204-17.

Barnett R, Raszkowski D, Winckler T, Stallforth P (2017) A versatile synthesis of the signaling peptide glorin. *Beilstein J Org Chem* 13, 247-250.

Barnett R, Stallforth P (2017) Natural products from social amoebae. *Chem Eur J* 24, 4202-4214.

MAJOR THIRD PARTY FUNDING

DFG: CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems – Project A4

DFG: SMABI – Sekundärmetabolite in Amöben-Bakterien Interaktionen

Fonds der Chemischen Industrie, VCI – Sachkostenbeihilfe

Dr. Illing Foundation: Bioaktive Naturstoffe in Amöben-Bakterien Interaktionen

Free State of Thuringia (EFRE): VITERAKT – Visualisierung von mikrobiellen Interaktionen und Infektionsmechanismen

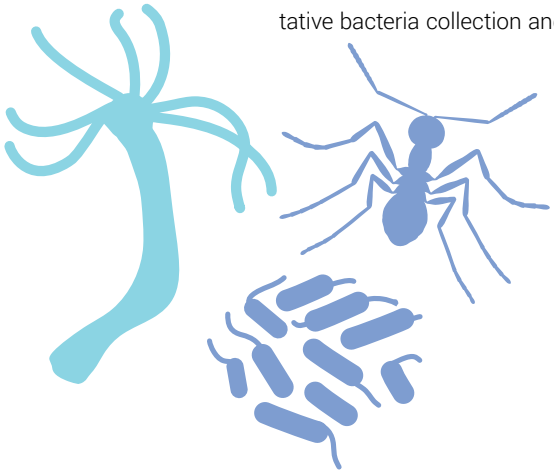
INDEPENDENT JUNIOR RESEARCH GROUP

CHEMICAL BIOLOGY OF MICROBE-HOST INTERACTIONS

INDEPENDENT JUNIOR RESEARCH GROUP
CHEMICAL BIOLOGY OF MICROBE-HOST INTERACTIONS

MOST IMPORTANT RESULTS

We selected the terrestrial fungus-growing termite and the marine hydroid polyp *Hydractinia echinata* as model systems. Fungus-growing termites rear a symbiotic fungus (Termitomyces) on fungus comb material as a food source. The termite gut and fungus comb are governed by a stable microbiota to assist in the defense and nutritional cycle. We focus (1) on the analysis of the chemical interactions between the mutualist (Termitomyces) and invading alien species to test the hypothesis that Termitomyces provides an important line of defence; (2) on the analysis of redox-active substances that are important for the oxidative lignin degradation via Fenton chemistry, and (3) on the defensive properties of associated bacteria. We established a representative bacteria collection and evaluated their antimicrobial properties. Ten strains were selected for genome sequencing (collaboration with the DSMZ, AK Kastner). HRMS-based dereplication of one strain revealed a novel group of secondary metabolites (rubterolones). We identified the putative gene cluster responsible for the biosynthesis (Guo *et al.* 2017), isolated several biosynthetic intermediates and performed precursor-directed modification of rubterolones. We have also investigated the co-evolved fungal antagonists (*Pseudoxylaria*) using fungus-fungus paired challenge assays and MS-based analysis led to the isolation of new cyclic tetrapeptides with an unusual allene modification (Guo *et al.* 2016). Precursor-directed analysis revealed a promiscuous NRPS machinery and afforded several novel derivatives. Finally, we have analyzed the chemical environment of the fungus comb using HRMS/MS to identify which compounds are responsible for the defensive properties of the comb material. We identified a core fungal metabolome within the comb, but also colony specific patterns.



The life cycle of the marine hydroid polyp *Hydractinia echniata* has a motile (larvae) and sessile reproductive phase (polyp). The metamorphosis is induced by compounds of associated bacterial species. (1) Based on our bacterial collection and activity studies, we selected fourteen strains for genome-sequencing and activity profiling (Rischer *et al.* 2016, Guo *et al.* 2017). *Pseudoalteromonas* strain P1-9 was selected for in-depth bioassay-guided fractionation and we identified three active substance(s). NMR-studies indicated a sugar- and a lipid-type of molecule, which might be responsible for the observed effect. Full structural elucidation is still ongoing. (2) We analyzed an associated *Cladosporium* species, and found three novel PKS-NRPS hybrid molecules, which are currently being investigated for their pharmacological activity. (3) To analyze the morphogenic properties of sulfonolipids, we have established a synthetic route to determine the absolute structure, install fluorescence tags and photoactive tags to identify the enzymatic target.

SELECTED COLLABORATIONS

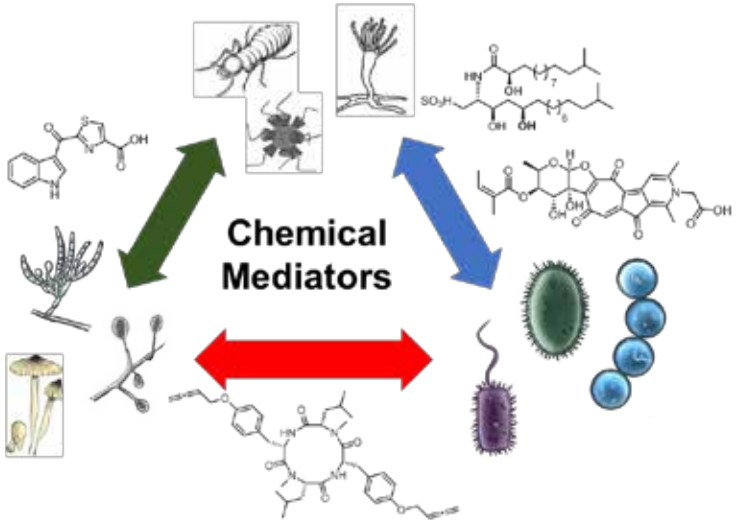
Clardy, Jon
Harvard Medical School, Boston, USA

Hadfield, Mike
University of Hawaii, Honolulu, USA

Hadfield, Mike
University of Pretoria, South Africa

Poulsen, Michael
University of Copenhagen, Denmark

Werz, Oliver
Friedrich Schiller University Jena, Germany



Within multi-partner associations, microbes secrete an array of chemically diverse small molecules to coordinate, influence and protect the system.

SELECTED PUBLICATIONS

Guo H, Kreuzenbeck NB, Otani S, Garcia-Altares M, Dahse HM, Weigel C, Aanen DK, Hertweck C, Poulsen M, Beemelmanns C (2016) Pseudoxylallemycins A-F, cyclic tetrapeptides with rare allenyl modifications isolated from *Pseudoxylaria* sp. X802: A competitor of fungus-growing termite cultivars. *Org Lett* 18, 3338-3341.

Guo H, Benndorf R, Leichnitz D, Klassen JL, Vollmers J, Görls H, Steinacker M, Weigel C, Dahse HM, Kaster AK, de Beer ZW, Poulsen M, Beemelmanns C (2017) Isolation, biosynthesis and chemical modifications of rubterolones A–F, rare tropolone alkaloids from *Actinomadura* sp. 5-2. *Chem Eur J* 23, 9338-9345.

Guo H, Rischer M, Sperfeld M, Weigel C, Menzel KD, Clardy J, Beemelmanns C (2017) Natural products and morphogenic activity of γ-Proteobacteria associated with the marine hydroid polyp *Hydractinia echinata*. *Bioorg Med Chem* 25, 6088-6097.

Leichnitz D, Raguž L, Beemelmanns C (2017) Total synthesis and functional analysis of microbial signalling molecules. *Chem Soc Rev* 46, 6330-6344.

Cantley AM, Woznica A, Beemelmanns C, King N, Clardy J (2016) Isolation and synthesis of a bacterially produced inhibitor of rosette development in choanoflagellates. *J Am Chem Soc* 138, 4326-4329.

MAJOR THIRD PARTY FUNDING

DFG: CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems – Project A06

DFG: EXSPHINGO – Erschließung und Totalsynthese von neuartigen mikrobiellen Sphingolipid-artigen Signalmolekulen

» THE ULTIMATE RESEARCH GOAL IS THE STRUCTURAL AND FUNCTIONAL ANALYSIS OF CHEMICAL MEDIATORS (DEFENSIVE, REDOX-ACTIVE, MORPHOGENIC, GROWTH MODULATING PROPERTIES) PRODUCED BY SYMBIOTIC MICROORGANISMS OF TWO MODEL SYSTEMS, THE FUNGUS-GROWING TERMITE SYSTEM AND THE COLONIAL HYDROID POLYP *HYDRACTINIA ECHINATA*. «

Christine Beemelmanns

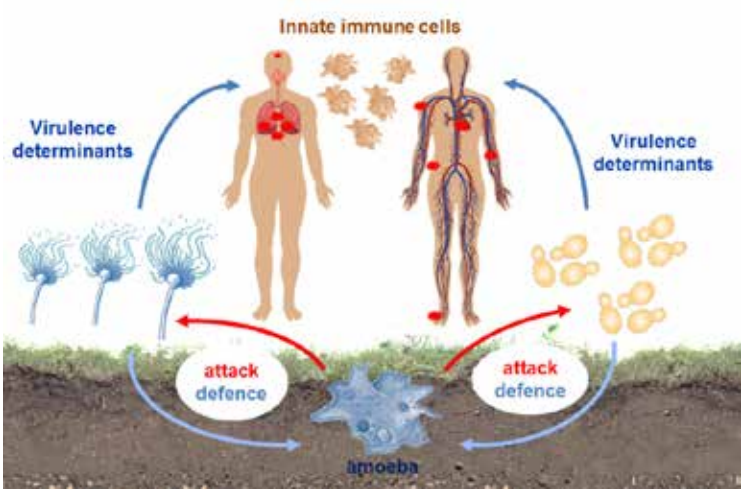
INDEPENDENT JUNIOR RESEARCH GROUP

EVOLUTION OF MICROBIAL INTERACTIONS

INDEPENDENT JUNIOR RESEARCH GROUP
EVOLUTION OF MICROBIAL INTERACTIONS

MOST IMPORTANT RESULTS

The rise in the number of life-threatening fungal infections over the past years poses several clinical and basic scientific challenges. Not only is the number of therapeutic and diagnostic options very limited for this group of organismens, but there is also scarce knowledge on what acutally causes certain fungi to be harmful for humans and warmblooded animals while others are rarely reported as pathogens. From an evolutionary perspective it seems very likely that at least some basic virulence determinants of human pathogenic fungi may have been shaped through ancient prey-predator relationships (Novohradská *et al.* 2017).



Predation by mycophagous amoeba could have imposed a selection pressure on environmental fungi to acquire traits which have later supported resistance to innate immune cells.

The group investigates the intrinsic resistance of major fungal pathogens like *Aspergillus* sp. and *Candida* sp. against phagocytosis using environmental amoeba as natural phagocytes. In collaboration with Dr. Matthias Brock, University of Nottigham, UK, the group demonstrated that intact surface structures of the infectious conidia of *A. terreus* are essential to escape from phagocytic uptake by the model amoeba *D. discoideum* (Geib *et al.* 2016). How fungal conidia are precisely processed in *D. disocoideum* is subject of ongoing work. A collaboration with Prof. Thierry Soldati was established and supported by an EMBO short term fellowship granted to Iuliia Ferling who spent three month at the University of Geneva, Switzerland.

Reactive oxygen species (ROS) are key mediator molecules during phagocyte-prey interactions and their role as killing or signalling molcules is controversially discussed, especially with regard to fungal pathogens. In a collaborative work with partners from the Leibniz-HKI and the US, the group could show for the first time that a single protein of *A. fumigatus* functionally connects sensitivity towards ROS with virulence in a mouse model of fungal infection (Hillmann *et al.* 2016). Work to unravel the specific *in vivo*-function of the protein, as well as the cellular targets of ROS is currently ongoing.

As the model amoeba *D. discoideum* naturally feeds on bacteria, the organism has only a limited capacity to study recognition and phagocytic killing of fungi. To overcome this drawback, the group has recently isolated a pureley fungivorous amoeba, *Protostelium aurantium*, estab-

» THE MISSION OF THIS RESEARCH UNIT IS TO EXPLOIT FUNGIVOROUS AMOEBA AS MICROBIAL PREDATORS TO IDENTIFY VIRULENCE DETERMINANTS OF FUNGAL PATHOGENS AND ELUCIDATE THE KILLING MECHANISMS OF ENVIRONMENTAL PHAGOCYTES. «

Falk Hillmann

lished its laboratory cultivation and sequenced its genome (Spaller *et al.* 2016; Hillmann et al. 2017). The amoeba feeds specifically on a wide range of pathogenic fungi and current projects are devoted to analyze if amoeba predation imposes selection pressure on genes involved in fungal virulence.

SELECTED COLLABORATIONS

Glöckner, Gernot
University of Cologne, Germany

Munder, Thomas
Ernst-Abbe-Hochschule, University of Applied Sciences, Jena, Germany

Paulus, Gerhard
Friedrich Schiller University Jena, Germany

Soldati, Thierry
University Genf, Switzerland

Winckler, Thomas
Friedrich Schiller University Jena , Germany

SELECTED PUBLICATIONS

Novohradská S, Ferling I, Hillmann F (2017) Exploring virulence determinants of filamentous fungal pathogens through interactions with soil amoebae. *Front Cell Infect Microbiol* 7, 497.

Geib E, Gressler M, Viediernikova I, Hillmann F, Jacobsen ID, Nietzsche S, Hertweck C, Brock M (2016) A non-canonical melanin biosynthesis pathway protects *Aspergillus terreus* conidia from environmental stress. *Cell Chem Biol* 23, 587-597.

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Vaknin Y, Hillmann F, Iannitti R, Ben Baruch N, Sandovsky-Losica H, Shadkchan Y, Romani L, Brakhage A, Kniemeyer O, Osherov N (2016) Identification and characterization of a novel *Aspergillus fumigatus* rhomboid family putative protease RbdA involved in hypoxia sensing and virulence. *Infect Immun* 84, 1866-1878.

MAJOR THIRD PARTY FUNDING

DFG: Die Bedeutung reduktiver Enzyme zur Abwehr gegen die oxidative Inaktivierung primärer Stoffwechselwege in *Aspergillus fumigatus*

Free State of Thuringia (ESF): Researcher Group MIQWI – Mikrobielle Interaktionen als Quelle für neue antiinfektive Wirkstoffe

Free State of Thuringia (EFRE): VITERAKT – Visualisierung von mikrobiellen Interaktionen und Infektionsmechanismen

CROSS-SECTIONAL UNIT

ILRS – INTERNATIONAL LEIBNIZ RESEARCH SCHOOL

CROSS-SECTIONAL UNIT **ILRS – INTERNATIONAL LEIBNIZ RESEARCH SCHOOL**

The first Alumni Meeting of ILRS and JSMC graduates took place in June 2016.

The *International Leibniz Research School for Microbial and Biomolecular Interactions* (ILRS) as graduate school of the HKI offers cutting edge doctoral research projects in close collaboration with the Friedrich Schiller University Jena, the University Hospital Jena and the Max Planck Institute for Chemical Ecology. Currently, around 60 doctoral researchers from 15 different countries pursue their PhD projects in microbiology, natural product chemistry, infection biology, bioinformatics or systems biology within the framework of ILRS. Since 2014, all doctoral researchers at the HKI benefit from the structured graduate training.

The ILRS curriculum consists of:

- Annual symposia and regular group seminars
- Annual Thesis Committee Meetings with the team of mentors
- Practical courses in advanced scientific techniques offered by ILRS faculty members
- An extensive selection of transferable skills courses, career orientation seminars and language courses
- Presenting the ILRS research topics to the public (e.g. during the Long Night of Sciences or Pupils' Resarch Day)
- Social activities for informal exchange and networking.

The ILRS closely works together with the other graduate schools in the field of microbiology in Jena under the umbrella of the excellence graduate school *Jena School for Microbial Communication* (JSMC). At the occasion of the 10th anniversary of ILRS and JSMC, in 2017 the first Alumni Meeting took place. Former graduates talked about their jobs in academia or industry and discussed career prospects with current members.

In 2016, the ILRS held its first Joint Meeting together with the Research Training Group (RTG) 1870: Bacterial Respiratory Infections in Wittenberg, with posters and talks by doctoral researchers from both graduate schools.

ILRS doctoral researchers not only publish their results in renowned journals, they also frequently receive external recognition for their work. The individual contributions are listed in the sections of the respective structural units.

All information about the projects, events and news are available on the ILRS website at **www.ilrs.de**.

ILRS JENA
MIBINTACT

» THE ILRS OFFERS EXCELLENT STRUCTURED GRADUATE TRAINING FOR DOCTORAL RESEARCHERS, COMBINING AMBITIOUS RESEARCH PROJECTS WITH A STATE-OF-THE-ART QUALIFICATION PROGRAMME IN LABORATORY METHODS AND TRANSFERABLE SKILLS. «

Peter F. Zipfel

ILRS SCIENTIFIC ADVISORY BOARD

Bringmann, Gerhard
Julius Maximilians University Würzburg, Germany

Hammerschmidt, Sven
University of Greifswald, Germany

Dersch, Petra
Helmholtz Centre for Infection Research, Braunschweig, Germany

Riesbeck, Kristian
Lund University, Malmö, Sweden

ILRS STEERING COMMITTEE

Zipfel, Peter F. (spokesperson)
Leibniz-HKI

Baldwin, Ian T.
Max Planck Institute for Chemical Ecology, Jena, Germany

Beemelmanns, Christine
Leibniz-HKI

Diekert, Gabriele
Friedrich Schiller University, Jena, Germany

Hube, Bernhard
Leibniz-HKI

Hoffmeister, Dirk
Friedrich Schiller University, Jena, Germany

ILRS REPRESENTATIVES

Esken, Jens
Friedrich Schiller University, Jena, Germany

Hanf, Benjamin
Leibniz-HKI

ILRS teamed up with the RTG Bacterial Respiratory Infections to hold a joint meeting for doctoral researchers from the two thematically-related graduate schools.

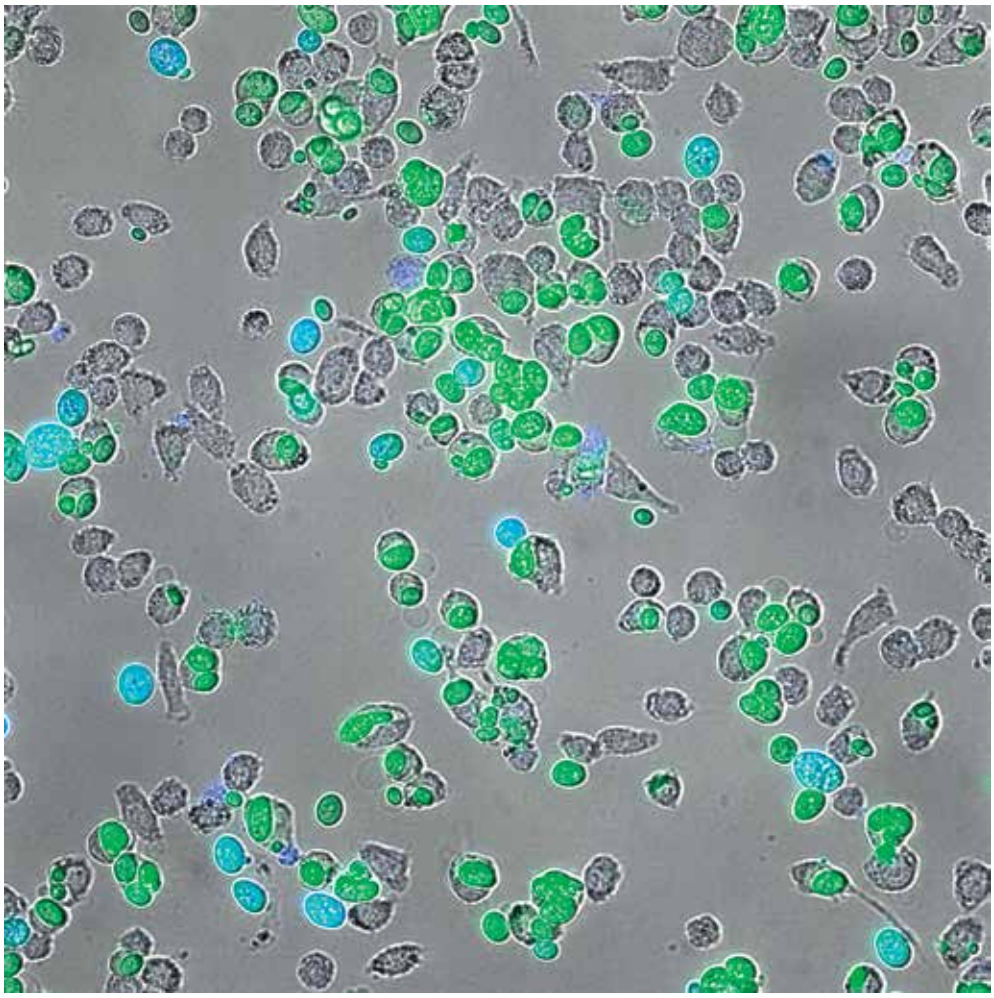
CROSS-SECTIONAL UNIT

JMRC – JENA MICROBIAL RESOURCE COLLECTION

CROSS-SECTIONAL UNIT
JMRC – JENA MICROBIAL RESOURCE COLLECTION

MOST IMPORTANT RESULTS

Mucormycosis is a life-threatening disease that affects in particular immune-deficient patients particularly. In this study, two strains of *L. corymbifera* species were used which were shown to be virulent or attenuated by various infection models (invertebrate, avian, mammalian) in our previous studies. Our earlier work confirmed that the protein surface structures of spores played a vital role in interacting with murine alveolar macrophages of the cell line MH-S, which encouraged us to proceed with the proteomic analysis of the spore surfaces of both strains. A difference in the abundance of protein candidates between the virulent and attenuated strains was observed. Among those proteins the hydrophobic surface binding protein A (HsbA) ranges among the most abundant ones and is therefore the main focus of our study. HsbA was first characterized as an adhesive factor in *Aspergillus oryzae* and in the insect-killing ascomycete *Beauveria bassiana* as a virulence factor for host insects. In our work, two copies of the HsbA protein were selected for further studies. They were chosen based on the difference in their distribution on the surface of both spores. One candidate of the HsbA protein was successfully heterologously overexpressed in *Pichia pastoris* and another one was synthetically designed. Polyclonal antibodies for both proteins, as well as monoclonal antibodies for over-expressed candidate proteins were developed. The specificity of antibodies was confirmed by western blots. The distribution of proteins on the surface of spores, germlings and hyphae were studied by fluorescence-activated cell scanning (FACS) and confocal laser scanning (CLSM) microscopy. Both proteins have the capability of blocking the phagocytic processes during the interaction of *Lichtheimia* spores with MH-S. Interestingly, HsbA has a large stimulatory effect on toll-like receptors (TLRs). Additionally, we could prove the ability of *Lichtheimia* to inhibit the apoptosis and phagolysosomal fusion in alveolar macrophages, whilst HsbA proteins don't have a detectable role in this process. Moreover, we found that HsbA proteins don't influence the acidification processes. The binding assay for HsbA proteins with various immune cell lines was carried out by using different antibodies (His-tag antibodies, polyclonal and monoclonal antibodies). From the host side, we also identified the receptors that may contributed to the recognitionpathogenesis on the



Interaction of spores of human pathogenic mucoralean fungi with murine alveolar macrophages: internal (phagocytosed) spores in green and external (adherent) spores in blue.

macrophage surface. Our initial results revealed that the heat shock protein HSP70 receptors on the surface of MH-S can bind and recognize the *Lichtheimia* spores. HSP70 seems to have a role in phagocytosis processes. Further studies on HSP70 are ongoing to investigate and characterize the role of HSP70 in pathogenesis processes. Our studies will have remarkable contribution to the understanding of the interaction of mucoralean fungi with MH-S. »

» THE MAIN GOAL OF THE JMRC IS BIPARTITE IN TERMS OF RESEARCH AND SERVICE: (1) -OMICS BASED INFECTION BIOLOGY DURING THE INTERPLAY BETWEEN *LICHTHEIMA CORYMBIFERA* AND INNATE IMMUNE CELLS AND (2) STORAGE, MAINTENANCE AND WORLD-WIDE EXCHANGE OF MICROORGANISMS, NATURAL PRODUCTS AND RESEARCH DATA. «

Kerstin Voigt

SELECTED PUBLICATIONS

Krieg R, Jortzik E, Goetz AA, Blandin S, Wittlin S, Elhabiri M, Rahbari M, Nuryyeva S, Voigt K, Dahse HM, Brakhage A, Beckmann S, Quack T, Grevelding CG, Pinkerton AB, Schönecker B, Burrows J, Davioud-Charvet E, Rahlfs S, Becker K (2017) Arylmethylamino steroids as novel antiparasitic agents. *Nat Commun* 8, 14478.

Becker T, Pasteels J, Weigel C, Dahse HM, Voigt K, Boland W (2017) A tale of four kingdoms - isoxazolin-5-one- and 3-nitropropanoic acid-derived natural products. *Nat Prod Rep* 34, 343-360.

Schulze B, Rambach G, Schwartze VU, Voigt K, Schubert K, Speth C, Jacobsen ID (2017) Ketoacidosis alone does not predispose to mucormycosis by *Lichtheimia* in a murine pulmonary infection model. *Virulence* 8, 1657-1667.

Steiniger C, Hoffmann S, Mainz A, Kaiser M, Voigt K, Meyer V, Süssmuth RD (2017) Harnessing fungal nonribosomal cyclodepsipeptide synthetases for mechanistic insights and tailored engineering. *Chem Sci* 8, 7834-7843.

Paetz C, Hammerbacher A, Menezes RC, Feistel F, Weigel C, Voigt K, Schneider B (2016) Chemical composition and antimicrobial activity of *Populus nigra* shoot resin. *Nat Prod Com* 11, 989-992.

MAJOR THIRD PARTY FUNDING

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project A6

BMBF: Zygonet – Etablierung eines europäischen Forschungsnetzwerks über humanpathogene Zygomyceten

BMBF: Silencing of genes encoding pathogenicity factors in zygomycetes

CROSS-SECTIONAL UNIT

NATIONAL REFERENCE CENTER FOR INVASIVE FUNGAL INFECTIONS

CROSS-SECTIONAL UNIT
NATIONAL REFERENCE CENTER FOR INVASIVE FUNGAL INFECTIONS

MOST IMPORTANT RESULTS

Due to our steadily growing network of partnering diagnostic institutions, the number of analysed clinical samples from patients with invasive fungal infections (IFI) all over Germany rose to 560 in 2017. All clinical isolates were identified using molecular reference methods. In most cases susceptibility testing was performed using EUCAST microdilution protocols. All identified strains are stored in the stock collection of the NRZMyk which is part of the Jena Microbial Resource Collection (JMRC). Beside identification and testing of clinical isolates, molecular detection of fungal pathogens in tissue samples is a major part of the NRZMyk work. For this, a portfolio of species- or group-specific PCRs as well as universal fungal PCRs has been established.

In addition to offering reference diagnostics beyond routine methods, the NRZMyk pursues application-oriented research projects. In a DFG funded project the taxonomic structure of Mucoraceae is revisited. Together with partners from Halle, Leipzig and Dresden the development of azole resistance in *Aspergillus fumigatus* in the environment is analysed in the BMBF funded project FINAR coordinated by the NRZMyk. Within FINAR, we developed an online database FunResDB to retrieve information on resistance mutations in *A. fumigatus* (Weber *et al.* 2017).

Due to its taxonomic expertise, the NRZMyk acts as reference laboratory for the ring trial "indoor mould fungi" of the Health Authority Baden Wuerttemberg. Furthermore, the NRZMyk maintains close contacts to numerous European mycological reference centers as well as to relevant committees of the ESCMID and the ISHAM. Prof. Kurzai acts as German representative of the Antifungal Susceptibility Testing of the EUCAST and as representative of the DMykG in the National Antibiotics Sensitivity Test Committee (NAK) involved in standardizing mycological test procedures. The NRZMyk has been appointed as EUCAST AFST (antifungal susceptibility testing) network laboratory for yeasts and moulds.

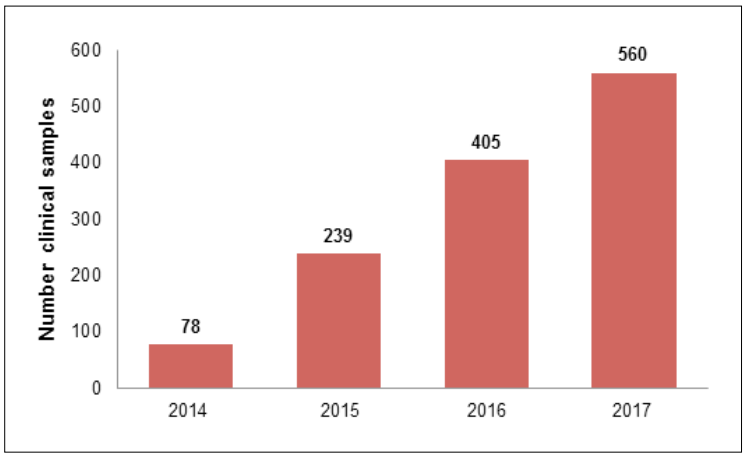
With regard to epidemiology of IFI in Germany the NRZMyk cooperates with FungiScope, a worldwide register for rare fungal infections (Prof. O. Cornely, University Hospital Cologne) and AlertsNet 2.0, a Thuringian wide prospective population based register to record nosocomial blood stream infections (Prof. F. Brunkhorst, UKJ). In addition, a national register for mycotic keratitis was established in cooperation with the Department of Ophthalmology of the University Hospital Düsseldorf. A first study with 22 cases of fusarium keratitis of otherwise healthy patients revealed that the eye infections correlated with wearing soft contact lenses (Walther *et al.* 2017). With the emergence of *Candida auris*, an intrinsically resistant *Candida* sp. that has caused several hospital outbreaks worldwide, we sent out information newsletters and are closely collaborating with the RKI to identify new cases as early as possible.

SELECTED PUBLICATIONS

Weber M, Schaer J, Walther G, Kaerger K, Steinmann J, Rath PM, Spiess B, Buchheidt D, Hamprecht A, Kurzai O (2017) FunResDB-A web resource for genotypic susceptibility testing of *Aspergillus fumigatus*. *Med Mycol* 56, 117-120.

Walther G, Stasch S, Kaerger K, Hamprecht A, Roth M, Cornely OA, Geerling G, Mackenzie CR, Kurzai O, von Lilienfeld-Toal M (2017) Fusarium Keratitis in Germany. *J Clin Microbiol* 55, 2983-2995.

Habbe KJ, Frings A, Schrader S, Roth M, MacKenzie C, Walther G, Kurzai O, Geerling G (2017) *Tintelnotia destructans*: ein neuer Feind vor dem Tore. [*Tintelnotia destructans*: new enemy at the gates]. *Der Ophtalmologe 115, 948-950.*



Since the establishment of NRZMyk at the HKI in 2014 the number of processed samples has been steadily increasing.

MAJOR THIRD PARTY FUNDING

BMG/Robert Koch-Institut: National Reference Center for Invasive Fungal Infections (NRZMyk)

» THE NRZMYK IS THE CENTRAL CONTACT POINT FOR DIAGNOSTICS AND THERAPY OF INVASIVE FUNGAL INFECTIONS IN GERMANY. IN ADDITION TO TARGETED CONSULTATION AND SPECIAL DIAGNOSTIC SERVICES WE AIM TO IMPROVE THE CLINICAL MANAGEMENT OF IFI AND SHARE OUR EXPERTISE WITH OUR NATIONAL AND INTERNATIONAL PARTNERS. «

Oliver Kurzai

CROSS-SECTIONAL UNIT

TRANSFER GROUP ANTIINFECTIVES


P4

CROSS-SECTIONAL UNIT
TRANSFER GROUP ANTIINFECTIVES

MOST IMPORTANT RESULTS

In the course of our activities, many new compounds from different academic partners and inhouse facilities were fully evaluted in terms of antimicrobial and antiviral activities (with the Friedrich-Loeffler-Institut as partner), cell line toxicity, physicochemical and pharmacological parameters. On this basis novel scaffolds with potential antifungal, antimycobacterial and anti-Gram-negative activity were revealed, which have recently entered medicinal chemistry programs within our group. For the appropriate pharmacological profing of compounds a new analytical platform was established which allows the quantitative determination and elucidation of bioactive ingredients and their degradation products in complex biological matrices at trace levels through a combination of high resolution mass spectrometry, UHPLC and radiodetection. Furthermore, a unique setup for the bioanalytical sample preparation of oxygen and temperature sensitive biological material was constructed.

During the late preclinical development of the antimycobacterial benzothiazinone BTZ043 (joint development program with Prof. Dr. Michael Hölscher, LMU Munich, partner site of the German Center for Infection Research (DZIF)) pronounced inconsistencies of the apparent drug concentrations were observed during pharmacokinetic studies in minipigs. Thus, we developed analytical methods which enabled the detection of all degradation products and found that a particularly unstable metabolite (M2) of BTZ043 is responsible for the drastic variation of the previously used bioanalytical methods. Through chemical attempts, we were succesful in producing authentic material of the putative metabolite and could show that M2 is a hydride Meisenheimer complex produced in vivo which readily oxidizes back upon formation of BTZ043 which explains the high deviations in drug concentration previously detected. To our knowledge hydride Meisenheimer complexes are completely unkown as degradation products of drugs. As M2 occurs at high levels in vivo, we suspected that M2 formation should have a drastic impact on the pharmacological properties of benzothiazinones. Through a chemical derivatization strategy and implementation of a newly developed MS-based assay we were able to show that the metabolic properties of benzothiazinones can be efficiently tuned. These results provide new rationales for the development of a new metabolically engineered generation of benzothiazinones and led to the implementation of a new research group (starting 2018).

For the preliminary assessment of the ADME of BTZ043, a cannulated bile study in the rat was performed and customized analytical methods were developed.

In view of the clinical development of BTZ043 a GMP process for the phase I study material was successfully established with the support of HAPILA GmbH as well as a new drug formulation by a subcontractor including all necessary documentation for IMPD submission.

The clinical candidate BTZ043 against *Mycobacterium tuberculosis* is extensively reduced *in vivo* to an oxygen sensitive hydride Meisenheimer complex. This type of metabolic transformation is fully unprecedented for drugs and drug candidates and provides a new starting point for rational lead development.

SELECTED COLLABORATIONS

Es-Sayed, Mazen
Bayer AG (Crop Science), Monheim, Germany

Hardt, Wolf-Dietrich
ETH Zurich, Zürich, Switzerland

Heimbach, Dirk
Bayer AG (Animal Health), Monheim, Germany

Hölscher, Michael
Hospital of the Ludwig-Maximilians-University Munich, Germany

Makarov, Vadim
A.N. Bach Institute of Biochemistry, Moskau, Russia

Menge, Christian
Friedrich Loeffler Institute, Jena, Germany

Miller, Marvin
University of Notre Dame du Lac, Notre Dame, USA

Müller, Uwe
HAPILA GmbH, Gera

» THE MISSION OF THE TRANSFER GROUP ANTIINFECTIVES IS THE ADVANCEMENT OF NOVEL ANTIMICROBIAL TECHNOLOGIES THROUGH MEDICINAL CHEMISTRY AND PHARMACOLGICAL ASSESSMENT IN ORDER TO DEFINE NEW LEADS AND PRECLINICAL DRUG CANDIDATES. «

Florian Kloß

SELECTED PUBLICATIONS

Kloss F, Krchnak V, Krchnakova A, Schieferdecker S, Dreisbach J, Krone V, Möllmann U, Hoelscher M, Miller M J (2017) *In vivo* dearomatization of the potent antituberculosis agent BTZ043 via Meisenheimer complex formation. *Angew Chem Int Ed* 56, 2187-2191.

Hoffmann B, Svensson C-M, Straßburger M, Gebser B, Irmler IM, Kamradt T, Saluz HP, Figge MT, (2017) Automated quantification of early bone alterations and pathological bone turnover in experimental arthritis by *in vivo* PET/CT imaging. *Sci Rep* 7, 2217.

Svensson C-M, Hoffmann B, Irmler I, Straßburger M, Figge MT, Saluz HP, (2017) Quantification of arthritic bone degradation by analysis of 3D micro-computed tomography data. *Sci Rep* 7, 44434.

Hillmann F, Bagramyan K, Straßburger M, Heinekamp T, Hong TB, Bzymek KP, Williams JC, Brakhage AA, Kalkum M (2016) The crystal structure of peroxiredoxin Asp f3 provides mechanistic insight into oxidative stress resistance and virulence of *Aspergillus fumigatus. Sci Rep* 6, 33396.

Kniemeyer O, Ebel F, Krüger T, Bacher P, Scheffold A, Luo T, Strassburger M, Brakhage AA (2016) Immunoproteomics of *Aspergillus* for the development of biomarkers and immunotherapies. *Proteomics Clin Appl* 10, 910-921.

MAJOR THIRD PARTY FUNDING

Free State of Thuringia (EFRE): BioChrom; Bioanalytische Methodenplattform zur pharmazeutischen Entwicklung antibiotischer Wirkstoffe

BMBF InfectControl 2020: New antiinfection strategies – Science • Society • Economy – BTZ-Met-ID

BMBF InfectControl 2020: New antiinfection strategies – Science • Society • Economy – Transsektorale Transferguppe Antiinfektiva

BMBF/DZIF: Preparation and conduct of phase I studies of BTZ043 as antibiotic TB drug

ASSOCIATED GROUP

HOST-FUNGAL-INTERFACES


MAXISAFE 2020

ASSOCIATED GROUP
HOST-FUNGAL-INTERFACES

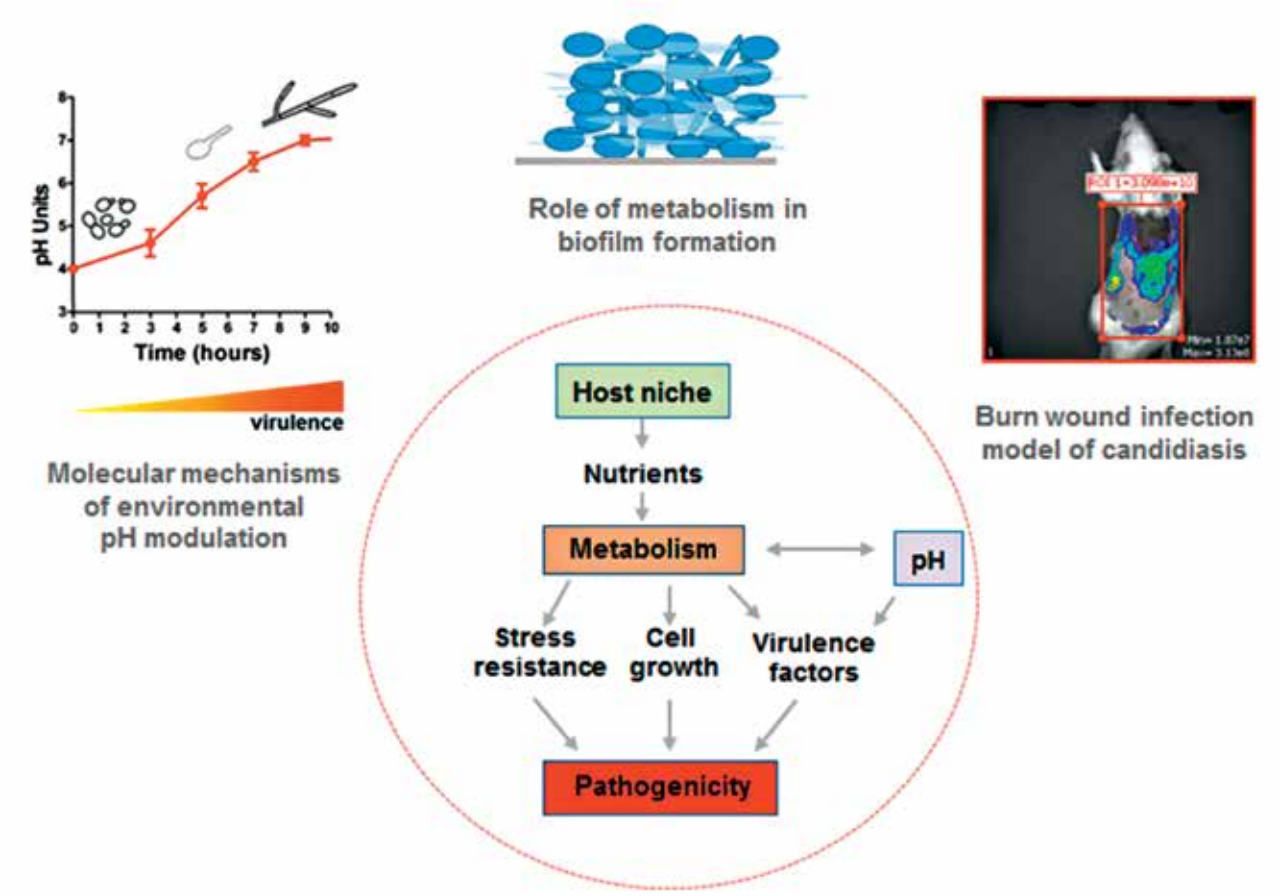
MOST IMPORTANT RESULTS

Metabolism is integral to *Candida* spp. pathogenicity, as it provides the platform for nutrient assimilation and growth in diverse host niches, affects fungal susceptibility to stress conditions and antifungal drugs, the expression of key virulence factors, and vulnerability to innate immune defenses. In *Candida albicans* these effects are driven by complex regulatory networks linking metabolism, morphogenesis and stress adaptation, all contributing to its success as a commensal and infectious agent. *C. albicans* hyphae are more virulent and yeast to hyphae transition can be promoted by various factors, including neutral pH. Recently we have shown that *C. albicans* can utilize host-relevant alternative carbon sources, such as amino acids (AA), to release ammonia from the cells, resulting in neutralization of extracellular pH and hyphal morphogenesis (Vylkova *et al.* 2011). This process occurs both *in vitro* and within the macrophage phagosome, where it contributes to hyphal growth and escape of the fungus from the immune cells (Vylkova and Lorenz 2014; 2017). Thus, utilization of host-derived carbon sources increases fungal virulence. Our goal is to understand the mechanism behind this phenomenon and its role on persistence of pathogenic Candida spp. in the host.

In *C. albicans* AA metabolism and ammonia release are controlled by the transcription factor Stp2. Another transcription factor, Ahr1, has been linked to AA metabolism and Stp2 regulation. Thus, we aim to delineate the relationship between Ahr1 and Stp2 in AA utilization and more globally. Further, we will evaluate the role of Ahr1 and Stp2 in alkalinization-driven hyphal morphogenesis. Currently, we analyse the transcriptome of Stp2 and Ahr1 deletion mutants upon growth on AA and in hyphae-inducing conditions. Next, we aim to elucidate the promoter occupancy of Stp2 and Ahr1 on target genes. To identify the factors involved in alkalinization-driven hyphal growth, we analyse the transcriptional responses during active pH modulation. In addition, we investigate the role of protein kinases in alternative carbon metabolism within the scope of the DFG-funded CRC/TR FungiNet.

C. albicans forms biofilms on biotic and abiotic surfaces. Adherence to form biofilms is Ahr1-regulated and mature biofilms are linked to activation of alternative carbon metabolism and hyphal growth. We aim to test if ambient pH and the metabolic state of the cells play role in biofilm growth. In this approach we develop microscopy- and microelectrode-based techniques to obtain spatial and temporal pH profiles of biofilms. Further, we establish a Bioflux device-based method to measure biofilm formation under native flow conditions.

C. albicans biofilms are frequently associated with burn wound infections. The virulence determinants and host responses in the course of infection will be evaluated by an *in vivo* burn wound model of candidiasis. As a complementary approach we will develop a “skin on a chip” wound infection model. »



Role of metabolism and active pH modulation in *Candida albicans* pathogenesis. *Candida albicans* metabolism plays an important role for survival of the fungus in the host and for pathogenicity. Utilization of some host-derived nutrients, such as amino acids, leads to rise of environmental pH. As neutral pH is a trigger for hyphal morphogenesis, a potent virulence factor in *C. albicans*, we aim to identify the molecular mechanisms and processes linked to pH modulation. *C. albicans* cells can form biofilm on biotic and abiotic surfaces, such as burn/severe wounds and catheters. Currently, we are evaluating the metabolic and pH profile of growing biofilms, and establishing a novel burn wound model of candidiasis using 3D tissue and animal models.

» HOST FUNGAL INTERFACES HAS BEEN ESTABLISHED WITHIN THE ZIK SEPTOMICS TO FOCUS ON RESPONSES OF PATHOGENIC *CANDIDA* SPP., WITH MAJOR FOCUS ON *CANDIDA ALBICANS*, TO METABOLIC AND PH CHANGES IN THE ENVIRONMENT, AND THE ROLE OF THESE FACTORS ON FUNGAL COLONIZATION AND INFECTIVITY. «

Slavena Vylkova

SELECTED COLLABORATIONS

Huebinger, Ryan
University of Texas Southwestern, Dallas, TX, USA

Krachler, Anne-Marie
University of Texas Health, Houston, TX, USA

Lorenz, Michael
University of Texas Health, Houston, TX, USA

Morschhäuser, Joachim
Julius Maximilians University Würzburg, Germany

Norrby-Teglund, Anna
Karolinska Institute, Stockholm, Sweden

SELECTED PUBLICATIONS

Vylkova S (2017) Environmental pH modulation by pathogenic fungi as a strategy to conquer the host. *PLoS Pathog* 13, e1006149.

Vylkova S and Lorenz MC (2017) Phagosomal neutralization by the fungal pathogen *Candida albicans* induces macrophage pyroptosis. *Infect Immun* 85, pii: e00832-16.

Danhof HA*, Vylkova S*, Vesely E, Ford AS, Gonzalez-Garay M, Lorenz MC (2016) Robust environmental alkalinization by *Candida albicans* during growth on dicarboxylic acids. *MBio* 7, pii: e01646-16. *contributed equally

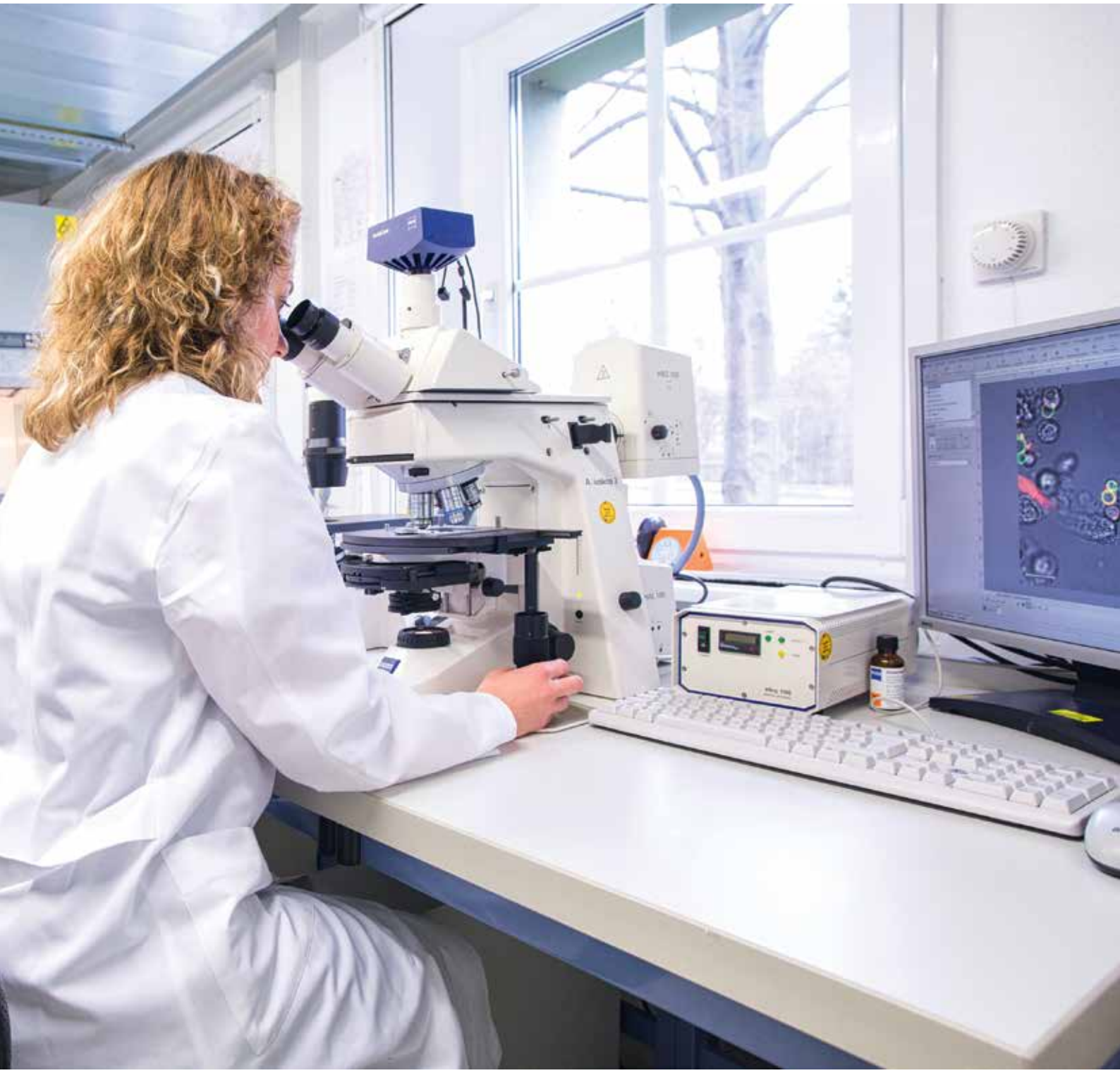
MAJOR THIRD PARTY FUNDING

BMBF: Unternehmen Region – „Zentren für Innovationskompetenz: Exzellenz schaffen – Talente sichern“ – Centre for Innovation Competence (ZIK) Septomics, Junior Research Group Host Fungal Interfaces

DFG: CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction – Project C2

ASSOCIATED GROUP

INFECTIONS IN HEMATOLOGY / ONCOLOGY



ASSOCIATED GROUP
INFECTIONS IN HEMATOLOGY / ONCOLOGY

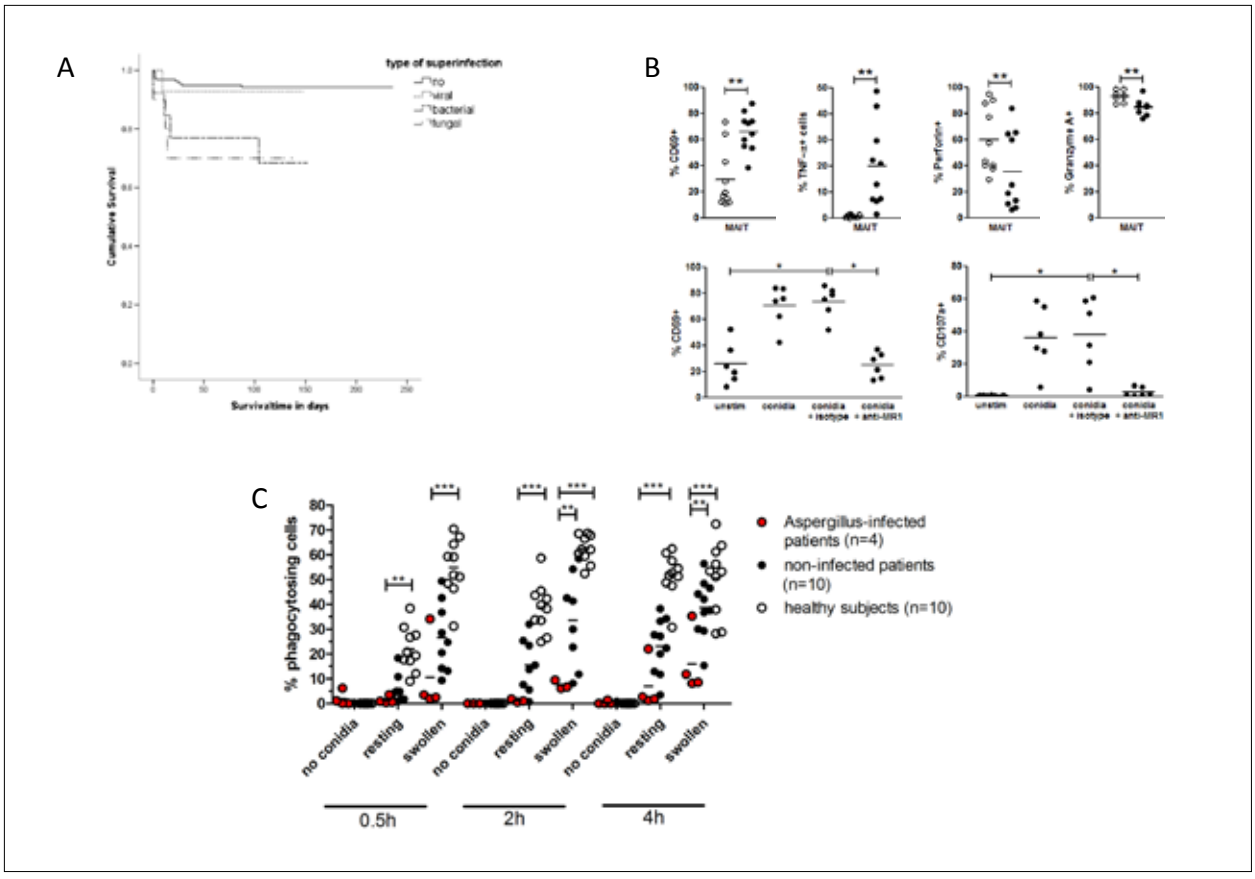
MOST IMPORTANT RESULTS

(1) Epidemiology of fungal and viral infections: In cooperation with the NRZMyk a national surveillance on Fusarium keratitis was conducted and published as described elsewhere (Walther *et al.* 2017). In addition to the epidemiology of fungal infections, one focus of our clinical research is the epidemiology of infections with community acquired respiratory viruses (CRV) in healthy persons or in patients with cancer (von Lilienfeld-Toal *et al.* 2016). Here, we finished a national project on the outcome of influenza infections in cancer patients identifying bacterial and fungal superinfection as the most prominent riskfactor for adverse outcome (figure 1A, Hermann *et al.* 2017). This has prompted the establishment of a national registry on CRV, which is currently underway.

(2) Bacterial infections: Bacterial infections remain a major threat in patients with therapy-induced neutropenia and require salvage antibiotic treatment in a large proportion of patients. In a diagnostic pilot study our group could identify subtherapeutic concentrations of the antibiotic piperacillin as a possible cause of treatment failure to treatment (Rachow *et al.* 2017). Consequently, a clinical trial investigating the effect of adapting the dose of piperacillin is currently recruiting in the department of Hematology and Medical Oncology (EudraCT Nr. 2016-002388-33). This trial as well as the above mentioned research on CRV is in line with the proposed research topics in the field of infections in neutropenic patients as outlined by the European Haematology Association (EHA) in their recent Roadmap (Engert *et al.* 2016).

(3) Immunology of fungal infections: Mucosal associated invariant T cells (MAIT) are innate-like T cells (TC) which are known to be activated by several bacteria and viruses, but activation by fungal pathogens such as the opportunistic human pathogen *Aspergillus fumigatus* is not well described. We could demonstrate that in contrast to conventional CD4+ and CD8+ TC, MAIT cells are activated by *A. fumigatus* in a TCR dependent manner and responded quickly with production of cytokines (TNF-a and IFN-g) and release of cytolytic proteins like perforin and granzyme (figure 1B, Jahreis *et al.* 2017). These findings add a new player to antifungal immunity and reveal MAIT cells as an interesting new effector in antifungal defense.

Neutrophilic granulocytes of immunosuppressed patients after allogenic hematopoetic stem cell transplantation show significantly impaired phagocytosis of *Aspergillus fumigatus* conidia, particularly if they are derived from patients who suffered from an invasive aspergillosis (figure 1C). Conidia with alterations of surface structures due to mutation in single GPI-anchored cell wall molecules also exhibited a different behaviour with regard to phagocytosis and adhesion. »



A In a cohort of 203 cancer patients with influenza, bacterial or fungal superinfection was the most important independent risk factor for mortality

B Human PBMC were co-cultured for 4 hours with A. *fumigatus conidia* and TC response was analysed by flow cytometry. MAIT cells upregulated CD69 and TNF-a as well as degranulation marker CD107a, while cytolytic proteins decreased. Blocking of TCR signaling with anti-MR1 prevented MAIT activation by fungal conidia

C The ability to phagocytose *A. fumigatus* conidia (resting state or pre-swollen for 4 hours) of neutrophilic granulocytes in patients after hematopoetic stem cell transplantation, especially in those with aspergillosis, was significantly reduced compared to healthy individuals during a coincubation for a half, two or four hours.

» THE WORKING GROUP IHO FOCUSES ON TRANSLATIONAL RESEARCH REGARDING INFECTIONS IN IMMUNOCOMPROMISED PERSONS. WE PERFORM CLINICAL AND EPIDEMIOLOGICAL RESEARCH INCLUDING CLINICAL TRIALS AS WELL AS LABORATORY BASED RESEARCH ADDRESSING THE IMMUNE RESPONSE AGAINST FUNGAL INFECTIONS. «

Marie von Lilienfeld-Toal

COLLABORATIONS

Lehners, Nicola
University Hospital Heidelberg, Germany

Mayer, Karin
University Hospital Bonn, Germany

Rieger, Christina
Ludwig Maximilians University Munich, Germany

Schalk, Enrico
University Hospital Magdeburg, Germany

Vehreschild, Maria
University Hospital Cologne, Germany

SELECTED PUBLICATIONS

Walther G, Stasch S, Kaerger K, Hamprecht A, Roth M, Cornely OA, Geerling G, Mackenzie CR, Kurzai O, von Lilienfeld-Toal M (2017) Fusarium Keratitis in Germany. *J Clin Microbiol* 55, 2983-2995.

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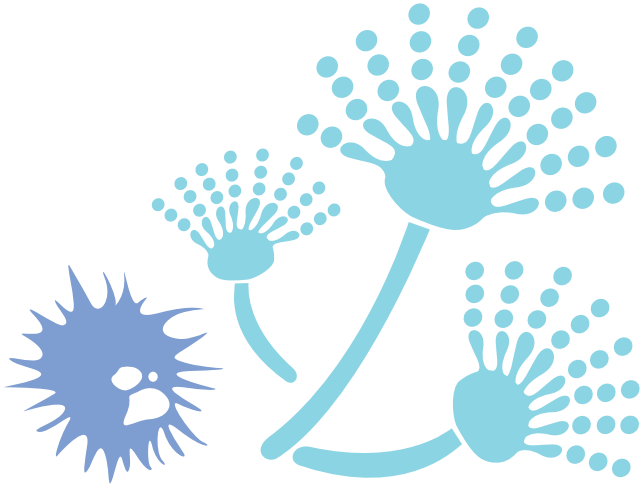
Hermann B, Lehners N, Brodhun M, Boden K, Hochhaus A, Kochanek M, Meckel K, Mayer K, Rachow T, Rieger C, Schalk E, Weber T, Schmeier-Jürchott A, Schlattmann P, Teschner D, von Lilienfeld-Toal M (2017) Influenza virus infections in patients with malignancies – characteristics and outcome of the season 2014/15. A survey conducted by the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO). *Eur J Clin Microbiol Infect Dis* 36, 565-573.

Engert A, Balduini C, Brand A, Coiffier B, Cordonnier C, Döhner H, de Wit TD, Eichinger S, Fibbe W, Green T, de Haas F, Iolascon A, Jaffredo T, Rodeghiero F, Salles G, Schuringa JJ (2016) EHA Roadmap for European Hematology Research. The European Hematology Association Roadmap for European Hematology Research: a consensus document. *Haematologica* 101, 115-208 (Section author "infections in neutropenic patients" Marie von Lilienfeld-Toal)

Jahreis S, Trump S, Bauer M, Bauer T, Thürmann L, Feltens R, Wang Q, Gu L, Grützmann K, Röder S, Averbeck M, Weichenhan D, Plass C, Sack U, Borte M, Dubourg V, Schüürmann G, Simon JC, von Bergen M, Hackermüller J, Eils R, Lehmann I, Polte T (2017) Maternal phthalate exposure promotes allergic airway inflammation over 2 generations through epigenetic modifications. *J Allergy Clin Immunol*, pii: S0091-6749(17)30570-5.

MAJOR THIRD PARTY FUNDING

BMBF: InfectoGnostics Research Campus – Patientenkohorte



ASSOCIATED GROUP

NETWORK MODELING

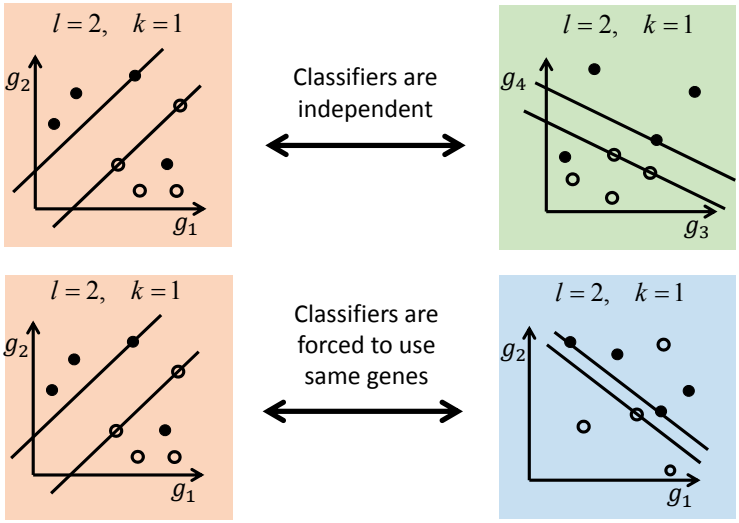
ASSOCIATED GROUP **NETWORK MODELING**

MOST IMPORTANT RESULTS

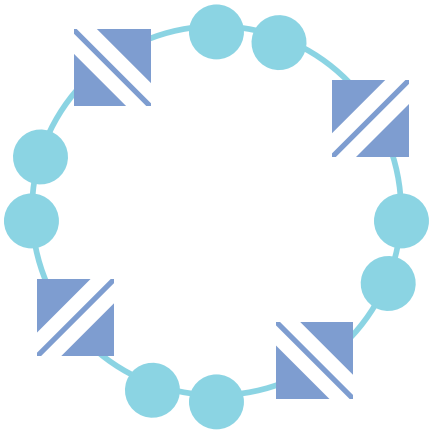
Our main focus is to understand the host response of systemic infection aiming to improve diagnosis and therapy. We investigate data from high throughput methods from functional genomics employing machine learning and network based models. In addition, we are developing and using our methods to investigate aberrant gene regulation of tumor cells. Methodologically, we develop and transfer Mixed Integer Linear Programming (MILP) based solutions into bioinformatics.

Blood stream infections can be caused by several pathogens such as viruses, fungi and bacteria. Appropriate and quick treatment is mandatory requiring rapid identification of the pathogen. Currently, pathogen identification relies on blood cultures which is too slow. Using gene expression profiles for machine learning enables to discriminate between types of infection, but also showed, so far, a high degree of inconsistency in the obtained biomarker lists. To produce consistent gene signatures, capable of discriminating fungal from bacterial infections, we combined SVM classifiers by joint optimization constraining them to the same set of discriminating features (Saraiva *et al.* 2016) (Figure 1). Employing this approach to discriminate between fungal and bacterial infection considerably increased the consistency of the biomarker list (Saraiva *et al.* 2017). Restricting the data to monocytes led to a gene signature enriched of lysosomal genes suggesting the lysosome genes to be specifically induced by fungal infection in monocytes. Real time qPCR of the identified lysosome-related genes confirmed the distinct gene expression increase in monocytes during fungal infections (Saraiva *et al.* 2017).

We aim for a mechanistic understanding of gene regulation. For this, we integrated MILP models into a comparative machine learning based approach to identify regulatory interactions that best explain the discrepancy of transcript levels in different types of samples as e.g. infected versus non-infected. Applying this new approach to telomerase transcript levels of yeast mutants with aberrant telomere length, we identified novel regulators of telomerase expression, several of which affect histone levels or modifications, particularly Sum1, Hst1 and Srb2 for the regulation of EST1, the effect of Sum1 was experimentally validated by cooperation partners (Poos *et al.* 2017). We compiled our method into a user



The upper two SVM classifiers maximize the margin independently from each other. The lower two maximize the sum of the two margins subject to that both use the same set of genes for the SVMs. Obviously the margins cannot increase but note that the overall SVM efficencies stay as good as before after applying these conditions.



friendly package for R (http://www.leibniz-hki.de/en/miprip.html). A similar approach was applied to identify SOX5 regulating MITF expression in skin cells (Kordass *et al.* 2016).

In addition, we investigated aberrant regulatory mechanisms of metabolism in tumor cells and revealed a hitherto unknown generic mechanism for large-scale metabolic reprogramming in cancer cells based on linear gene proximities between cancer-causing and enzyme coding genes (Sharma *et al.* 2016).

COLLABORATIONS

Bauer, Michael
University Hospital Jena, Germany

Eils, Roland
Ruprecht Karls University Heidelberg, Germany

Kupiec, Martin
Tel Aviv University, Tel Aviv, Israel

Löffler, Jürgen
Julius Maximilians University Würzburg, Germany

Rippe, Karsten
German Cancer Research Center, Heidelberg, Germany

SELECTED PUBLICATIONS

Saraiva JP, Oswald M, Biering A, Röll D, Assmann C, Klassert T, Blaess M, Czakai K, Claus R, Löffler J, Slevogt H, König R. (2017) Fungal biomarker discovery by integration of classifiers. *BMC Genomics* 18, 601.

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Kordaß T, Weber CEM, Oswald M, Ast V, Bernhardt M, Novak D, Utikal J, Eichmüller SB, König R. (2016) SOX5 is involved in balanced MITF regulation in human melanoma cells *BMC Medical Genomics* 9, 10.

Poos AM, Maicher A, Dieckmann AK, Oswald M, Eils R, Kupiec M, Luke B, König R (2016) Mixed Integer Linear Programming based machine learning approach identifies regulators of telomerase in yeast. *Nucleic Acids Research* 44, e93.

» SYSTEMIC INFECTION CAN CAUSE UNCONTROLLED IMMUNE RESPONSE FOLLOWED BY MULTIPLE ORGAN FAILURE LEADING TO SEPSIS AND OFTEN DEATH. OUR MISSION IS TO UNDERSTAND THE MOLECULAR CONTEXT OF THE HOST RESPONSE TO SYSTEMIC INFECTION TO IDENTIFY BIOMARKERS FOR DIAGNOSIS AND APPROPRIATE TREATMENT. «

Rainer König

ASSOCIATED GROUP

PHARMACEUTICAL MICROBIOLOGY

ASSOCIATED GROUP
PHARMACEUTICAL MICROBIOLOGY

MOST IMPORTANT RESULTS

Polyenes

A taxonomically undescribed stereaceous basidiomycete produces two branched-chain antilarval polyenes in response to mycelial injury. A candidate gene for a reducing polyketide synthase (PKS) was heterologously overexpressed in Aspergillus niger. Both polyenes were isolated from this host, and verified by NMR spectroscopy and imaging mass spectrometry. It was shown that this PKS has an unprecedented intrinsic activity to shift multiple double bonds. This is the first basidiomycete reducing PKS that was characterized.

Indole alkaloids

Psilocybin is the major natural product of the psychotropic so-called magic mushrooms. The genomes of Psilocybe cubensis and P. cyanescens were sequenced and a candidate gene cluster identified which encoded a monooxygenase, a kinase, a decarboxylase, and a methyltransferase (PsiH, PsiK, PsiD, and PsiM, respectively). By heterologous production of PsiD, PsiK, and PsiM, psilocybin production from 4-hydroxy-L-tryptophan was reconstituted in vitro. The substrate specificities of these enzymes suggest that psilocin (the dephosphorylation product and actual hallucinogenic agent) is not a biosynthetic intermediate. In-depth investigations on the natural product profile of Psilocybe mushrooms, combined with a refined extraction protocol, revealed that the previously reported psilocin contents are artifacts.

Hydroxamate siderophores

Countless basidiomycetes encode a peptide synthetase which represents the most conserved basidiomycete natural product enzyme. Its function has remained unclear, although its domain setup is suggestive of a siderophore synthetase. Using the respective cDNA from *Ceriporiopsis subvermispora*, this 274 kDa enzyme was heterologously produced in function-

» WE INVESTIGATE FUNGAL AND BACTERIAL NATURAL PRODUCTS. OUR MAIN FOCUS LIES ON THE BIOCHEMICAL AND GENETIC BASIS OF THEIR BIOSYNTHESES, EMPHASIZING BASIDIOMYCETE SECONDARY METABOLISM. WE ARE ALSO INTERESTED WHICH ROLE THESE METABOLITES PLAY FOR CHEMICAL ECOLOGY. «

Dirk Hoffmeister

Psilocybe cyanescens is a lignicolous mushroom and producer of psilocybin and other psychotropic indole alkaloids, whose biosynthesis was investigated at the Leibniz HKI.

al form in *Aspergillus niger*. It catalyzes trimerization of N5-acetyl-N5-hydroxy-L-ornithine into basidioferrin, a new natural product and siderophore backbone.

Pulvinic acids

The response of the model basidiomycete *Serpula lacrymans* (house eater mushroom) to the presence of bacterial consortia was investigated wthin the CRC ChemBioSys framework. Numerous bacteria, strongly induced the biosynthesis of atromentin, which is the central precursor to bioactive pulvinic acids, e.g., variegatic acid, which modulate swarming and biofilm formation of bacteria.

Sesquiterpene aryl esters

The research program on the melleolides, i.e., sesquiterpene aryl esters of Armillaria mellea (honey mushroom), was continued. Emphasis was put on the mode of action of the melleolides, both towards its extremely rapid cell death-inducing properties in mammalian cells and regarding its antifungal activity.

Lipopeptides

In close cooperation with Markus Nett (TU Dortmund), a project to explore the secondary metabolome of the bacterial plant pathogen Ralstonia solanacearum has been continued. Major results are the full structure elucidation of ralsolamycin, including its absolute configuration, of this complex lipopeptide. »

SELECTED COLLABORATIONS

Blanchette, Robert
University of Minnesota, Saint Paul, MN, USA

Goodell, Barry
Virginia Tech, Blacksburg, VA, USA

Keller, Nancy
University of Wisconsin, Madison, WI, USA

Künzler, Markus
ETH Zurich, Switzerland

Nett, Markus
Technical University Dortmund, Germany

SELECTED PUBLICATIONS

Brandenburger E, Gressler M, Leonhardt R, Lackner G, Habel A, Hertweck C, Brock M, Hoffmeister D (2017) A highly conserved basidiomycete peptide synthetase produces a trimeric hydroxamate siderophore. *Appl Environ Microbiol*, pii: AEM.01478-17.

Brandt P, Garcia-Altares M, Nett M, Hertweck C, Hoffmeister D (2017) Induced chemical defense of a mushroom by a double bond-shifting polyene synthase. *Angew Chem Intl Ed* 56, 5937-5941.

Fricke J, Blei F, Hoffmeister D (2017) Enzymatic synthesis of psilocybin. *Angew Chem Intl Ed* 56, 12352-12355.

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Tauber J, Schroeckh V, Shelest, E, Brakhage AA, Hoffmeister D (2016) Bacteria induce pigment formation in the basidiomycete *Serpula lacrymans*. *Environ Microbiol* 18, 5218-5227.

MAJOR THIRD PARTY FUNDING

DFG: CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems – Project B05

DFG: Der Substratspezifitäts-Code von Peptidsynthetasen aus Basidiomyceten.

DFG: Biochemical and genetic basis of indole alkaloid formation in the basidiomycete *Psilocybe cyanescens*.

ASSOCIATED GROUP

SYNTHETIC MICROBIOLOGY

ASSOCIATED GROUP
SYNTHETIC MICROBIOLOGY

MOST IMPORTANT RESULTS

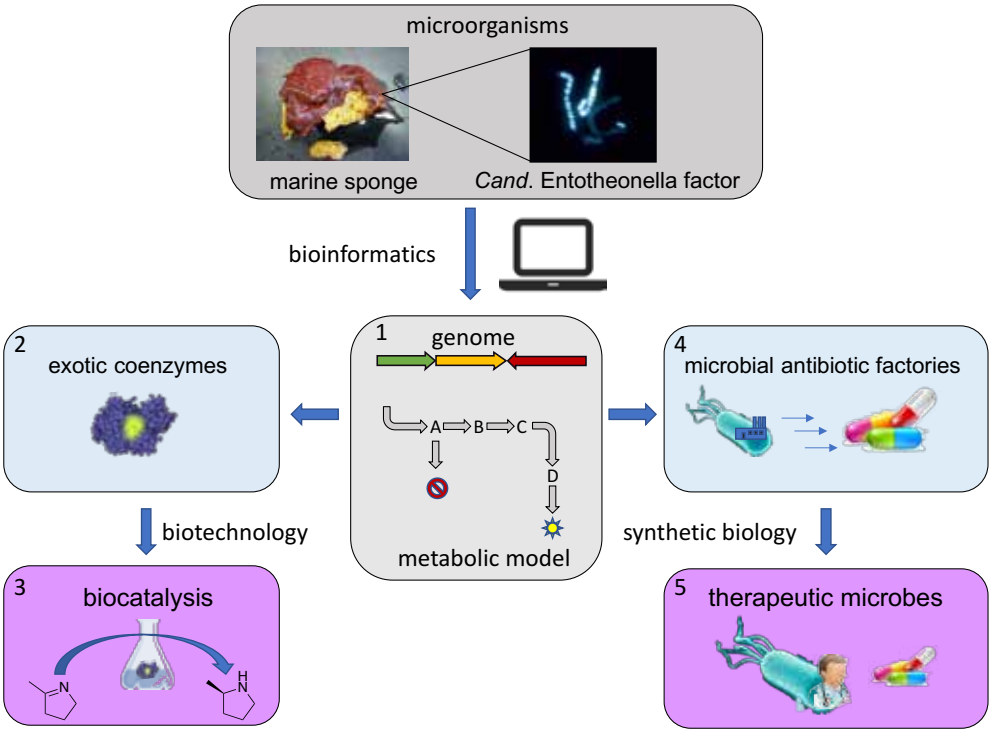
Together with Prof. Jörn Piel (ETH Zurich), we have analyzed the genomes of as-yet uncultured bacteria that live in stable symbiosis with marine sponges. These bacteria called "*Candidatus* Entothenella factor" have attracted considerable interest as producers of a plethora of natural products known from sponges, including potent toxins and anti-cancer compounds. We have found that Entotheonella bacteria have highly complex genomes that mirror specialized biochemical pathways. One interesting prediction we could make from genome and proteome analyses is that *Cand.* E. factor is able to consume methanol as a carbon source and requires rare earth metals like lanthanum as trace elements for methanol utilization. This result might help to cultivate these valuable bacteria in the future.

Furthermore, we have shown that Entotheonella species encode a huge number of enzymes that require rare organic cofactors like coenzyme F420. Coenzymes are small molecules supporting the catalytic activity of enzymes and are thus highly important for biocatalysis. Together with Prof. Christian Hertweck, we found that coenzyme F420 is also relevant for bacterial symbionts of mold fungi. These discoveries lead us to the idea to engineer a safe, stable microbial source for coenzyme F420 procurement in order to further investigate enzymes- and processes dependent thereof to finally make them accessible to biocatalysis applications.

We have also contributed to a study of Prof. Dirk Hoffmeister on a conserved enzyme of mushrooms (a nonribosomal peptide sythetase). The team could show that the multidomain enzyme, whose function had been elusive since more than a decade, actually produces a siderophore (an iron-carrier), another important group of bioactive natural products.

» WE USE SYNTHETIC BIOLOGY TO ENGINEER BACTERIA TO PRODUCE BIOACTIVE MOLECULES. WE CURRENTLY EXPLOIT RARE MICROBIAL COFACTORS FOR BIOCATALYSIS APPLICATIONS. WE ALSO DEVELOP THERAPEUTIC MICROBES, I.E. SYMBIOTIC BACTERIA THAT DIAGNOSE DISEASES AND CURE THEM BY PRODUCTION OF PHARMACEUTICALS. «

Gerald Lackner



1 The junior research group Synthetic Microbiology studies natural product-producing bacteria like the as-yet uncultured symbiont of marine sponges *Candidatus* Entotheonella factor.

2 Starting from (meta-)genome sequencing the metabolic capacities of a microbe will be predicted by bioinformatics.

3,4 One focus is on rare and novel cofactors, which will be tested for biotechnological applications.

5 Biosynthesis gene clusters are cloned to produce valuable molecules in "microbial antibiotic factories".

6 Finally, antibiotics production is integrated into designed therpaeutic microbes that sense and cure diseases by the release of specific antibiotics.

We have ongoing projects to discover novel bioactive natural products, especially novel cofactors from Mycobacteria and we are working on the integration of natural product biosyntheses into designed beneficial microbes. Our vision is that engineered commensal bacteria dwelling in the human microbiome diagnose diseases in the human body and cure them *in situ* by production of appropriate pharmaceuticals like antibiotics. This concept is called "therapeutic microbes" or, more metaphorically, "microbial physicians".

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Lackner G, Peters EE, Helrich EJ, Piel J (2017) Insights into the lifestyle of uncultured bacterial natural product factories associated with marine sponges. *Proc Natl Acad Sci USA* 114, E347-E56.

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MAJOR THIRD PARTY FUNDING

Free State of Thuringia (EFRE): Chip-to-World – System für die Entdeckung und miniaturisierte Bioprozessentwicklung neuer Naturstoffe

FACTS AND FIGURES


WERNESGRÜNER

ORGANIZATION OF THE HKI
ORGANISATION DES HKI

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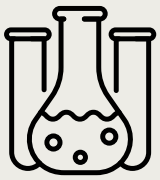
HKI AT A GLANCE **DAS HKI AUF EINEN BLICK**



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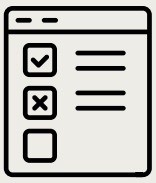

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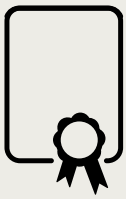

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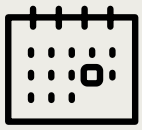

19
Scientific Colloquia at the Leibniz-HKI
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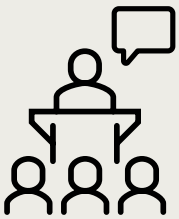

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Organisation of Scientific Meetings and Conferences

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Netzwerke und Verbundprojekte

Media Reports
Medienberichte
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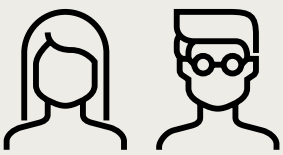
10 TV und Hörfunk

20,4 Mio Euro
Third Party Funding
Drittmittelfinanzierung



439[2]
Employees
Mitarbeiter

[1] Beteiligung an 27, davon 10 am Leibniz-HKI koordiniert

[2] 31.12.2017

INVENTIONS AND PATENTS
ERFINDUNGEN UND SCHUTZRECHTE

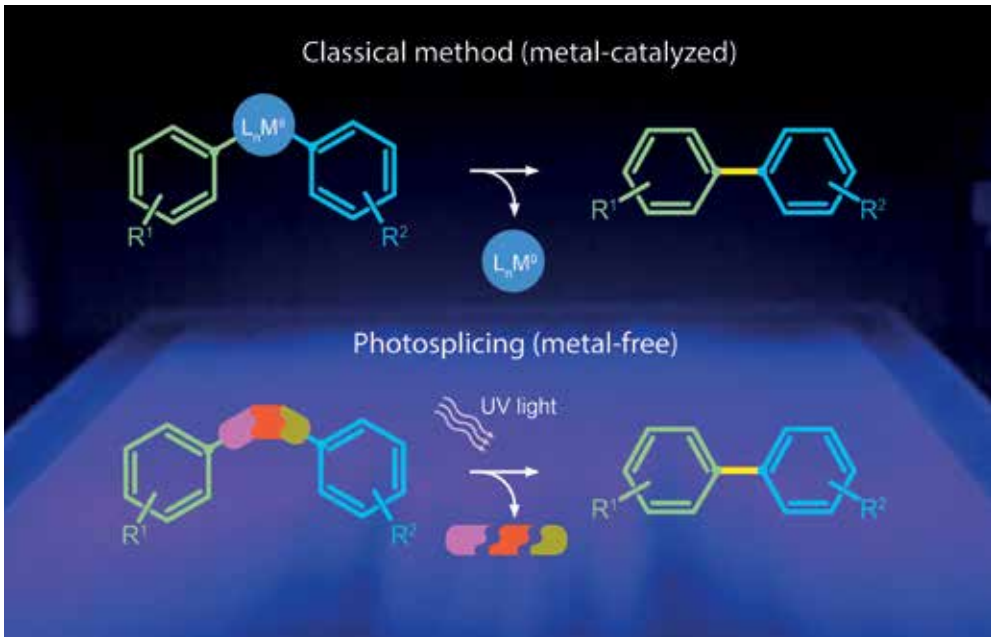
Schutzrechte sind neben Originalpublikationen in referierten Fachjournalen ein wesentlicher Leistungsparameter für die Forschungsarbeit am HKI. Forschungsteams aus den Hauptforschungsfeldern des HKI, Naturstoff-Forschung und Infektionsbiologie, trugen ebenso wie Technologie-orientierte Gruppen im Zeitraum 2016/2017 mit einer Reihe von Erfindungen zum Schutzrechts-Portfolio des Instituts bei. Vom HKI angemeldete Patente führten zu einer Reihe fruchtbarer Industriekooperationen und bilden die Grundlage für anwendungsorientierte Drittmittelvorhaben.

Ein Team um Christian Hertweck fand im Genom des Bakteriums *Paraburkholderia graminis* Hinweise auf ein neuartiges Eisenaufnahmesystem. Die Forscher isolierten daraufhin ein ringförmiges Molekül, das zur Substanzfamilie der Lipodepsipeptide gehört. Es erhielt den Namen Gramibactin, da die Erzeugerbakterien mit den Wurzeln von Süßgräsern – den Gramineen – vergesellschaftet sind. Gramibactin fixiert Eisen(III)-Ionen mit sehr hoher Bindekraft. Als Bindungspartner dienen zwei ungewöhnliche N-Nitrosohydroxylamin-Gruppierungen, die aus der Ringstruktur herausragen und bislang noch nicht in natürlichen Eisentransportern beobachtet wurden. Dies macht Gramibactin zum ersten Vertreter einer neuen Klasse von Siderophoren. Die Forscher prüften, ob Gramibactin die Eisenversorgung von Pflanzen verbessern kann, in deren Nähe es vorkommt. Als Maß hierfür verwendeten Sie die Bildung von Chlorophyll, das nur dann synthetisiert werden kann, wenn genügend Eisen vorhanden ist. Tatsächlich bildeten Maispflanzen bis zu 50 % mehr Chlorophyll, wenn die Nährlösung den Gramibactin-Eisen-Komplex enthielt. Derzeit laufende Untersuchungen widmen sich der Frage, ob Gramibactin als natürlicher Wachstumsförderer in der Agrarwirtschaft in Frage kommt.

Im Zuge der präklinischen Entwicklung des am Leibniz-HKI entdeckten Tuberkulose-Antibiotikums BTZ-043 fiel auf, dass ein signifikanter Teil des Wirkstoffs *in vivo* reversibel zu einem unbekannten Metaboliten M2 reduziert wird. Detaillierte Untersuchungen des Teams um Florian Kloß zur Natur von M2 führten zu der völlig überraschenden Erkenntnis, dass es sich um einen sogenannten Meisenheimer-Komplex handelt. Derartige Verbindungen waren bislang nur aus der Synthesechemie, nicht jedoch aus der Natur bekannt. M2 bietet einen vielversprechenden Ausgangspunkt für die Entwicklung einer nächsten Generation potenter, resistenzbrechender Tuberkulosewirkstoffe mit verbesserten pharmakologischen Eigenschaften.

Im Rahmen einer Synthesestudie beobachteten Christian Hertweck und Kollegen, dass sich bestimmte ringförmige Moleküle – sogenannte *Bis*-Arylsulfonamide – bei Einwirkung von

The tuberculosis drug candidate BTZ-043 is reduced to a Meisenheimer complex in the presence of human cells.



Catalysts containing heavy metals (blue circle) are used for the classical synthesis of biaryls (top). The novel metal-free photosplicing technology (bottom) uses a sulfonamide linker, which breaks down to gaseous fragments when exposed to UV light.

UV-Licht in eine blau fluoreszierende Substanz umwandeln. Analysen ergaben, dass es sich bei dem Reaktionsprodukt um ein sogenanntes Biaryl handelt. Die Verknüpfung erfolgt dabei geometrisch hochselektiv, sodass trotz einer Vielzahl theoretischer Kombinationsmöglichkeiten ein nahezu reines Produkt in hoher Ausbeute entstand. Damit erfüllt die Sulfonamid-Gruppierung in Kombination mit UV-Licht in dem neuen Syntheseverfahren die gleiche Funktion wie bisher verwendete Schwermetall-Katalysatoren. Verunreinigungen des Produktes durch Spuren giftiger Metalle könnten auf diese Weise vermieden werden. Um die Übertragbarkeit der neuen Reaktion in einen größeren Maßstab zu prüfen, haben die Chemiker auch einen geeigneten Reaktor entworfen und unter der Bezeichnung Photosplicer praktisch realisiert. Die neue Photosplicing-Technologie weist nach ersten Untersuchungen eine große Anwendungsbreite auf. So stellten die Forscher eine ganze Reihe pharmazeutisch wichtiger Biaryle völlig metallfrei her. Darunter befanden sich auch Wirkstoffe von Blockbuster-Präparaten mit mehr als einer Milliarde US-Dollar Jahresumsatz, wie zum Beispiel Blutdrucksenker, Entzündungshemmer, Zytostatika, Schmerzmittel oder Wirkstoffe für neurodegenerative Erkrankungen.

Die Anmeldung neuer Schutzrechte unterliegt einer strengen hausinternen Evaluation und konzentriert sich auf neue, biologisch aktive Naturstoffe und deren (bio-)synthetische Derivate sowie vielversprechende Targets für die Diagnose und Therapie von Infektionskrankheiten. »

Young corn plants were treated with iron-free gramibactin (four leaves on the left) and with an iron-gramibactin complex. The darker green colour of the four leaves on the right shows that the plants can use the iron from the complex for the increased synthesis of chlorophyll.

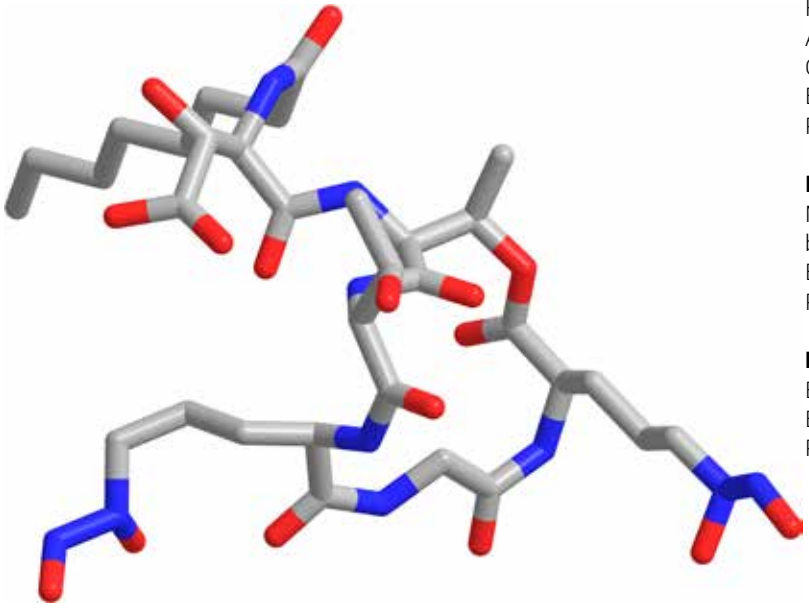
Besides original publications in peer-reviewed journals, intellectual property rights are an important performance parameter for research work at the HKI. Research teams from the main research fields of the HKI, natural product research and infection biology, as well as technology-oriented groups contributed a number of inventions to the institute's IP portfolio in the period 2016/2017. Patents applied for by the HKI have led to a number of fruitful industrial cooperations and form the basis for application-oriented third-party funding projects.

Christian Hertweck and his team found evidence of a novel iron uptake system in the genome of the bacterium *Paraburkholderia graminis*. The researchers isolated a ring-shaped molecule that belongs to the family of lipodepsipeptides and named it gramibactin because the bacteria that produce it are associated with the roots of sweet grasses – the Gramineae. Gramibactin fixes iron (III) ions with a very high affinity through two unusual N-nitrosohydroxylamine groups that protrude from the ring structure. This has not previously been observed in natural iron transporter molecules and thus makes gramibactin the first representative of an entirely new class of siderophores. The researchers tested whether gramibactin can improve the iron supply of plants in the vicinity of which it occurs, using the production of chlorophyll as a read-out. It could be demonstrated that corn plants produced up to 50 % more chlorophyll on exposure to the gramibactin-iron complex. Current investigations are focused on the question whether Gramibactin might be a natural growth promoter in agriculture.

In the course of the preclinical development of the tuberculosis antibiotic BTZ-043 discovered at the Leibniz-HKI, it was noticed that a significant part of the active substance is reversibly reduced *in vivo* to an unknown metabolite M2. Detailed investigations by Florian Kloß' team into the nature of M2 led to the completely surprising discovery that it is a so-called Meisenheimer complex. Such compounds were previously only known from synthesis chemistry, but not from nature. M2 offers a promising starting point for the development of a next generation of potent, resistance-breaking tuberculosis agents with improved pharmacological properties.

In a synthesis study, Christian Hertweck and colleagues observed that certain ring-shaped molecules, so-called bis-arylsulfonamides, convert into a blue fluorescent substance when exposed to UV light. Analyses revealed that the product of this reaction is a biaryl. The coupling is highly selective for the geometrical configuration, resulting in a high yield of a nearly pure reaction product, despite a multitude of theoretical combination possibilities. The sulfonamide linker in combination with UV light fulfils the same function as heavy metal catalysts used up to now. Contamination of the product by traces of toxic metals can thus be avoided. In order to demonstrate the transferability of this new reaction to a larger scale, the chemists have designed a suitable reactor, termed photosplicer. First investigations show a wide range of applications for this new photosplicing technology. The researchers were able to synthesize a range of pharmaceutically important biaryls without the use of heavy metals. Among them were active ingredients of blockbuster drugs with more than 1 billion USD annual turnover, such as antihypertensive agents, anti-inflammatories, cytostatic agents, pain relievers or active ingredients for neurodegenerative diseases.

A model of the molecule gramibactin.



The application for new intellectual property rights is subject to strict in-house evaluation and focuses on new, biologically active natural substances and their (bio-)synthetic derivatives as well as promising targets for the diagnosis and therapy of infectious diseases.

Roth M, **Peschel G**, **Bardl B**, **Perlet K**, **Martin K**, **Hoffmeier C**, **Steinacker M**, **Vollstädt S**, **Willing K**, König GM, Bouhired S, Kehraus S, Schäberle TF, Schmitz A
Verfahren zur Gewinnung von Corallopyronin A
PCT/EP2017/051335
Priority date 2016-01-21

Kloß F, **Schieferdecker S**, **Brakhage A**, **Wojtas P**, Möllmann U, Dreisbach J, Miller M
New antimicrobial compounds, their use for the treatment of mammalian infections and a new metabolic mechanism
EP16190199
Priority date 2016-09-22

Kloß F, **Wojtas P**
New antimicrobial compounds and their use in the treatment of mammalian infections
EP17192338
Priority date 2017-09-21

Kiehntopf M, Schwerler D, Kaczmarek A, **Horn U**
Antibody for the specific detection of CAAP47/48 fragments
EP17197139
Priority date 2017-10-18

Kloß F, **Neuwirth T**, **Haensch V**, **Hertweck C**
Method for the metal-free preparation of a biaryl by a photosplicing reaction and their uses
EP17202739
Priority date 2017-11-21

Hertweck C, **Ishida K**, **Hermenau R**
Bacterial siderophore gramibactin
EP17207667
Priority date 2017-12-15

EXTERNAL FUNDING
DRITTMITTEL

Participation in Research Networks | Beteiligung an Netzwerken und Verbundprojekten

EU

Opathy – From Omics to Patient: Improving Diagnostics of Pathogenic Yeasts
(Marie-Skłodowska-Curie Innovative Training Network (ITN))
Duration: 2015-2019
PI: Hube, Bernhard
Total funding: 238,000 €
Funding 2016/17: 159,000 €

QuantFung – Discovery of Streptomycetes induced fungal secondary metabolite formation
(Marie Curie Initial Training Network (ITN))
Duration: 2013-2017
PI: Brakhage; Axel
Total funding: 238,000 €
Funding 2016/17: 107,000 €

Leibniz Association

KAIT: Kryostress - Anpassungsmechanismen der Zelle an Tiefsttemperaturen
(Leibniz Competition)
Duration: 2013-2017
PI: Kniemeyer; Olaf
Total funding: 154,500 €
Funding 2016/2017: 31,500 €

Leibniz ScienceCampus InfectoOptics: Combating infectious diseases with advanced optical methods
(Leibniz ScienceCampus)
Duration: 2015-2018
PIs: Brakhage, Axel (spokesperson); Figge, Marc Thilo; Horn, Uwe; Hube, Bernhard; Jacobsen, Ilse; Kurzai, Oliver
Total funding: 386,219 €
Funding 2016/2017: 223,600 €

MikrOMIC: Die Rolle von Mikroplastik als Träger mikrobieller Populationen im Ökosystem Ostsee
(Leibniz Competition)
Duration: 2014-2017
PI: Hillmann; Falk
Total funding: 6,500 €
Funding 2016/17: 2,800 €

DFG

CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems
(Collaborative Research Center)
Duration: 2014-2018
PIs: Hertweck, Christian (spokesperson); Brakhage, Axel; Nett, Markus; Guthke, Reinhard; Shelest, Ekaterina
Total funding: 1,397,000 €
Funding 2016/17: 709,700 €

CRC 1192 Immune-Mediated Glomerular Diseases
Duration: 2016-2019
PI: Zipfel, Peter
Total funding: 408,500 €
Funding 2016/17: 201,300 €

CRC 1278 PolyTarget - Polymer-based nanoparticle libraries for targeted anti-inflammatory strategies
PIs: Brakhage, Axel; Figge, Marc Thilo
Duration: 2017-2021
Total funding: 633,500 €
Funding 2016/17: 75,900 €

CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction
(Collaborative Research Center / Transregio)
Duration: 2013-2017
PIs: Brakhage, Axel (spokesperson), Figge, Marc Thilo Guthke, Reinhard Hube, Bernhard; Jacobsen, Ilse; Kniemeyer, Olaf; Shelest, Ekaterina; Skerka, Christine; Voigt, Kerstin; Zipfel Peter F.
Total funding: 3,114,000 €
Funding 2016/17: 1,216,300 €

GSC 214 JSMC: Jena School for Microbial Communication
(Graduate School of Excellence)
Duration: 2007-2017
PIs: Brakhage Axel (spokesperson); Beemelmanns, Christine; Brock, Matthias; Figge, Marc Thilo; Guthke, Reinhard; Hertweck, Christian; Hillmann, Falk; Horn, Uwe; Hube, Bernhard; Jacobsen, Ilse; König, Rainer; Kurzai, Oliver; Lilienfeld-Toal, Marie; Nett, Markus; Saluz, Hans Peter; Shelest, Ekaterina; Stallforth, Pierre; Zipfel Peter F.
Total funding: 4,4323,000 €
Funding 2016/17: 988,500 €

SPP 1580: Intracellular compartments as places of pathogen-host-interactions
(Priority Programme)
Duration: 2011-2017
PI: Hube; Bernhard
Total funding: 296,950 €
Funding 2016/17: 165,000 €

BMBF

Advanced UV for Life
(Zwanzig20 – Partnerschaft für Innovation)
Duration: 2014-2020
PI: Saluz Hans Peter
Total funding: 401,014 €
Funding 2016/17: 401,014 €

Cancer-SYS – Analyzing gene regulatory networks in neuro- ectodermal tumors
Duration: 2013-2016
PI: König, Rainer
Total funding: 227,000 €
Funding 2016/17: 81,000 €

CSCC: Integrated Research and Treatment Centers Center for Sepsis Control and Care
Duration: 2011-2020
PIs: Brakhage, Axel; Kurzai, Oliver; Kniemeyer, Olaf; Jacobsen, Ilse; Hube, Bernhard; Zipfel, Peter F.
Total Funding: 1,621,000 €
Funding 2016/17: 260,300 €

EXASENS – POC-Sensorplattform für chronisch-entzündliche Atemwegserkrankungen (EXASENS
Duration: 2015-2018
PI: Kniemeyer, Olaf
Total funding: 361,700 €
Funding 2016/17: 241,000 €

FunComPath: Fungal Commensal-to-Pathogenicity
(ERA-Net Infect-ERA)
Duration: 2015-2018
PI: Hube, Bernhard
Total funding: 264,000 €
Funding 2016/17: 177,000 €

InfectControl 2020: New antiinfection strategies – Science • Society • Economy
(Zwanzig20 – Partnerschaft für Innovation)
Duration: 2014-2020
PIs: Brakhage, Axel (spokesperson); Kurzai, Oliver; Nett, Markus; Kniemeyer, Olaf; Guthke, Reinhard; Hertweck, Christian; Kloß, Florian
Total funding: 4,876,000 €
Funding 2016/17: 2,198,500 €

InfectoGnostics Research Campus
Duration: 2015-2020
PIs: Jacobsen, Ilse
Total funding: 590,500 €
Funding 2016/17: 248,200 €

LRC: Leibniz Research Cluster Bio/synthetic multifunctional micro production units – novel ways of compound development
(Strategy Process Biotechnology 2020+)
Duration: 2015-2020
PIs: Brakhage, Axel (spokesperson); Valiante, Vito
Total funding: 1,502,000 €
Funding 2016/17: 694,000 €

SPICE III – Einfluss von Meeresverschmutzung auf Biodiversität und den Lebensunterhalt von Küstenbewohnern
(Wissenschaftlich-Technische Zusammenarbeit mit Indonesien)
Duration: 2012-2016
PI: Saluz, Hans Peter
Total funding: 297,000 €
Funding 2016/17: 5,900 €

BMG/RKI

NRZMyk: National Reference Center for Invasive Mycoses
Duration: 2014-2019
PIs: Kurzai, Oliver; von Lilienfeld-Toal, Marie; Voigt, Kerstin
Total funding: 474,000 €
Funding 2016/17: 78,000 €

Free State of Thuringia

AutoScreen: Plattform für die multiparametrische Datenerfassung und -analyse in der tropfenbasierten Mikrofluidik zur Entwicklung von Ultrahochdurchsatz-Screening-Anwendungen für die Biotech-Industrie
(Thuringian Directive on the Promotion of Research, Technology and Innovation)
Duration: 2017-2020
PIs: Figge, Marc Thilo; Roth, Martin
Total funding: 335,600 €
Funding 2016/17: 26,000 €

DropCode: Microfluidic platform technology for ultra-high throughput screening of novel antimicrobial compounds from microorganisms
(Thüringen GreenTech)
Duration: 2014-2016
PIs: Figge, Marc Thilo; Roth, Martin
Total funding: 195,000 €
Funding 2016/17: 100,500 €

DZIF

BTZ043 a novel TB drug
Duration: 2015-2016
PI: Voigt, Kerstin
Total funding: 36,000 €
Funding 2016/17: 18,000 €

Innovative mikrobielle Quellen für neue Antiinfektiva
Duration: 2016-2018
PIs: Roth, Martin
Total funding: 197,100 €
Funding 2016/17: 131,400 €

Vorbereitung und Durchführung von Phase-I-Studien mit dem Antituberkulotikum BTZ043
Duration: 2017-2020
PI: Kloss, Florian
Total funding: 117.149,00 €
Funding 2016/17: 78,871 €

Leibniz Research Alliances

Bioactive Compounds and Biotechnology

Health Technologies

Infections'21: Transmission Control of Infections in the 21th Century

Individual Projects | Einzelvorhaben

EU

FUNBIT – Imaging Mass Spectrometry of Fungal-Bacterial Interplay
(Marie Sklodowska-Curie Actions - Individual Fellowships (IF))
Duration: 2016-2018
PI: García-Altares Pérez, María
Total funding: 171,500 €
Funding 2016/17: 145,800 €

BMBF

Gene silencing in human pathogenic zygomycetes
(Collaboration with Hungary)
Duration: 2014-2016
PI: Voigt, Kerstin
Total funding: 16,500 €
Funding 2016/17: 9,200 €

Zygonet – Etablierung eines europäischen Forschungsnetzwerks über humanpathogene Zygomyceten (ERA-Fellowship)
Duration: 2016
PI: Voigt, Kerstin
Total funding: 11,810 €
Funding 2016/17: 11,810 €

DFG

AfuInf - Proteom-und Polysaccharid-om-Analysen der initialen Infektionsphase von *Aspergillus fumigatus*
(Research Grant with Agence Nationale de la Recherche / The French National Research Agency)
Duration: 2016-2018
PI: Brakhage, Axel
Total funding: 311,000 €
Funding 2016/17: 51,800 €

CO2 Adaption in *Candida glabrata* and its role in host-pathogen interaction
(Research Grant)
Duration: 2013-2017
PI: Kurzai, Oliver
Total funding: 187,500
Funding 2016/17: 93,500 €

Deciphering the substrate specificity code of basidiomycete peptide synthetases
(Research Grant)
Duration: 2014-2017
PI: Hoffmeister, Dirk
Total funding: 187,600 €
Funding 2016/17: 117,600 €

Die Bedeutung reduktiver Enzyme zur Abwehr gegen die oxidative Inaktivierung primarer Stoffwechselwege in *Aspergillus fumigatus*
(Research Grant)
Duration: 2016-2018
PI: Hillmann, Falk
Total funding: 204,000 €
Funding 2016/17: 110,500 €

Die Faktor H-vermittelte Komplement-evasion des Malariaparasiten *Plasmodium falciparum*
(Research Grant)
Duration: 2016-2018
PI: Skerka, Christine
Total funding: 215,600 €
Funding 2016/17: 24,000 €

EXSPHINGO – Erschließung und Totalsynthese von neuartigen mikrobiellen Sphingolipid-artigen Signalmolekulen
(Research Grant)
Duration: 2016-2019
PI: Beemelmanns, Christine
Total funding: 352,800 €
Funding 2016/17: 124,000 €

Gottfried Wilhelm Leibniz Prize
PI: Hertweck, Christian
Total funding: 3,000,000 €
MorphPath: The Role of morphogenesis in the pathogenesis of systemic candidiasis
(Research Grant)
Duration: 2013-2016
PI: Jacobsen, Ilse
Total funding: 192,000 €
Funding 2016/17: 61,000 €

Novel molecular mechanismsof iron sensing and homeostasis in filamentous fungi
(D-A-CH Lead Agency Action)
Duration: 2014-2017
PIs: Brakhage, Axel, Hortschansky, Peter
Total funding: 366,000 €
Funding 2016/17: 201,000 €

Polyphasic taxonomic revision of Mucoraceae
(Research Grant)
Duration: 2014-2016
PI: Walther, Grit
Total funding: 159,000 €
Funding 2016/17: 105,700 €

Reduktion mikrobieller Adhäsion
(Research Grant)
Duration: 2016-2018
PI: Brakhage, Axel
Total funding: 208,300 €
Funding 2016/17: 138,800 €

SMABI – Sekundärmetabolite in Amöben-Bakterien Interaktionen
(Research Grant)
Duration: 2017-2020
PI: Stallforth, Pierre
Total funding: 200,600 €
Funding 2016/17: 27,900 €

12. VAAM Fachgruppentagung „Molekularbiologie der Pilze“
(International scientific meeting)
Duration: 2017
PI: Hillmann, Falk; Valiante, Vito
Total funding: 2,600 €
Funding 2017: 2,600 €

Leibniz Association

A Molecular Targeting Approach to Combat Human Pathogenic Fungi
(Leibniz Competition)
Duration: 2017-2020
PI: Hertweck, Christian
Total funding: 748,000 €
Funding 2016/17: 234,000 €

Free State of Thuringia (with means of the European Social Fund and the European Regional Development Fund):

Free State of Thuringia / European Social Fund

Miqwi – Mikrobielle Interaktionen als Quelle für neue antiinfektive Wirkstoffe
(Researcher Groups)
Duration 2016-208
PI: Hillmann, Falk
Total funding: 623,000 €
Funding 2016/17: 415,300 €

PiDOMICS – Pilzinfektionen: neue Verfahren zur Diagnose und zum Therapiemonitoring mit Hilfe von OMICS-Technologien und Bioinformatik
(Researcher Groups)
Duration 2017-2019
PI: Linde, Jörg
Total funding: 698,200 €
Funding 2016/17: 218,000 €

Free State of Thuringia / European Regional Development Fund

BioChrom – Bioanalytische Methodenplattform zur pharmazeutischen Entwicklung antibiotischer Wirkstoffe
(Thuringian Directive on the Promotion of Research)
Duration: 2017
PI: Kloß, Florian
Total funding: 99,500 €
Funding 2016/17: 99,500 €

Chip-to-World – System für die Entwicklung und miniaturisierte Bioprozessentwicklung neuer Naturstoffe -
(Thuringian Directive on the Promotion of Research)
Duration: 2016-2017
PI: Roth, Martin
Total funding: 492,000 €
Funding 2016/17: 492,000 €

FermDown – Integrierte Bioprozessentwicklung neuer Fermentations- und Produktreinigungsverfahren (Downstream Processing) von Naturstoffen
(Thuringian Directive on the Promotion of Research)
Duration: 2016-2017
PI: Horn, Uwe
Total funding: 526,700 €
Funding 2016/17: 526,700 €

MACWiP – Massenspektrometrische Charakterisierung der Wirt-Pilzpathogen Interaktion
(Thuringian Directive on the Promotion of Research)
Duration: 2016-2017
PI: Kniemeyer, Olaf
Total funding: 699,700 €
Funding 2016/17: 699,700 €

VITERAKT – Visualisierung von mikrobiellen Interaktionen und Infektionsmechanismen
(Thuringian Directive on the Promotion of Research)
Duration: 2016-2017
PI: Hillmann, Falk; Stallforth, Pierre
Total funding: 693,500 €
Funding 2016/17: 693,500 €

Other sources

Aventis Foundation

The Roles of Eukaryotic Polyketides in Interspecies Interactions of *Dictyostelium discoideum*
Duration: 2015-2017
PI: Stallforth, Pierre
Total funding: 49,000 €
Funding 2016/17: 42,000 €

Daimler and Benz Foundation

A Pipeline for Biosynthetic Engineering of Antibiotic Peptides
(Postdoc Fellowship)
Duration: 2016-2018
PI: Kries, Hajo
Total funding: 40,000 €
Funding 2016/17: 36,700 €

Deciphering the Chemical Communication Code in Symbiotic Eukaryote-Prokaryote Interactions
(Postdoc Fellowship)
Duration: 2014-2016
PI: Stallforth, Pierre
Total funding: 40,000 €
Funding 2016: 1,700 €

Exploring the Chemical Potential of Termite-associated Bacteria
(Postdoc Fellowship)
Duration: 2014-2016
PI: Beemelmanns, Christine
Total funding: 40,000 €
Funding 2016: 1,700 €

Deutscher Akademischer Austauschdienst

Graduate School Scholarship Programme
Duration: 2016-2017
PI: Zipfel, Peter
Total funding: 4 PhD fellowships

Deutsche Jose Carreras-Leukämiestiftung

Respiratory viruses in patients after allogeneic stem cell transplantation
Duration: 2015-2016
PI: von Lilienfeld-Toal, Marie
Total funding: 15,000 €
Funding 2016: 10,000 €

Dr. Illing-Stiftung

Bioaktive Naturstoffe in Amöben-Bakterien Interaktionen
Duration: 2016-2018
PI: Stallforth, Pierre
Total funding: 10,000 €
Funding 2016/17: 8,000 €

Humboldt Foundation

Capes Humboldt Research Fellowship for Postdoctoral Researchers
Duration: 2016-2017
PI: Pacheco Fill, Taicia
Total funding: 37,400 €
Funding 2016/17: 37,400 €

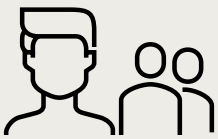
Humboldt Research Fellowship for Postdoctoral Researchers
Duration: 2016-2018
PI: Dunbar, Kyle
Total funding: 82,800 €
Funding 2016/17: 65,600 €

Fonds der chemischen Industrie

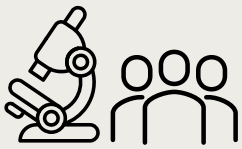
Support for workshop
Duration: 2016
PI: Beemelmanns, Christine; Stallforth, Pierre
Total funding: 5,000 €
Funding 2016: 5,000 €

STAFF **MITARBEITER**

9
Professors
Professoren



8
Group Leaders
Gruppenleiter



57
Research Associates
Wissenschaftliche Mitarbeiter

102
Doctoral Researchers
Doktoranden

40
Bachelor and Master Students
Bacheloranden und Masteranden

75
Non-scientific Employees
Nichtwissenschaftliches Personal

55 %
Female Employees
Frauenanteil

2
Trainees
Auszubildende

24 %
International Employees
Internationale Mitarbeiter

Status 31.12.2017

PEER REVIEWED ARTICLES
ORIGINALARBEITEN

Department Biomolecular Chemistry

Barnes EC, **Jumpathong J**, Lumyong S, Voigt K, **Hertweck C** (2016) Daldionin, an unprecedented binaphthyl derivative, and diverse polyketide congeners from a fungal orchid endophyte. *Chemistry* 22(13), 4551-4555.

Chankhamjon P, **Tsunematsu Y**, **Ishida-Ito M**, Sasa Y, **Meyer F**, **Boettger-Schmidt D**, **Urbansky B**, Menzel KD, **Scherlach K**, Watanabe K, **Hertweck C** (2016) Regioselective dichlorination of a non-activated aliphatic carbon atom and phenolic bismethylation by a multifunctional fungal flavoenzyme. *Angew Chem Int Ed* 55(39), 11955-11959.

Chizzali C, Gusberti M, Schouten HJ, Gessler C, Broggini GA (2016) Cisgenic Rvi6 scab-resistant apple lines show no differences in Rvi6 transcription when compared with conventionally bred cultivars. *Planta* 243(3), 635-644.

De Felice A, Di Lorenzo F, **Scherlach K**, **Ross C**, Silipo A, **Hertweck C**, Molinaro A (2016) Structural investigation of the lipopolysaccharide O-chain isolated from *Burkholderia fungorum* strain DSM 17061. *Carbohydr Res* 433, 31-35.

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Franke J, **Hertweck C** (2016) Biomimetic thioesters as probes for enzymatic assembly lines: Synthesis, applications, and challenges. *Cell Chem Biol* 23(10), 1179-1192.

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Heine D, **Sundaram S**, Beudert M, Martin K, **Hertweck C** (2016) A widespread bacterial phenazine forms conjugates with biogenic thiols and crosslinks proteins. *Chem Sci* 7, 4848-4855.

Horn F, Linde J, Mattern DJ, Walther G, Guthke R, **Scherlach K**, Martin K, Brakhage AA, Petzke L, Valiante V (2016) Draft genome sequences of fungus *Aspergillus calidoustus*. *Genome Announc* 4(2), e00102-16.

Kröber A, **Scherlach K**, Hortschansky P, Shelest E, Staib P, Kniemeyer O, Brakhage AA (2016) HapX mediates iron homeostasis in the pathogenic dermatophyte *Arthroderma benhamiae* but is dispensable for virulence. *PLOS One* 11(3), e0150701.

Kumpfmüller J, Methling K, Fang L, Pfeifer BA, Lalk M, Schweder T (2016) Production of the polyketide 6-deoxyerythronolide B in the heterologous host *Bacillus subtilis*. *Appl Microbiol Biotechnol* 100(3), 1209-1220.

Richter ME, Neugebauer S, Engelmann F, Hagel S, Ludewig K, La Rosée P, Sayer HG, Hochhaus A, von Lilienfeld-Toal M, **Bretschneider T**, Pausch C, Engel C, Brunkhorst FM, Kiehntopf M (2016) Biomarker candidates for the detection of an infectious etiology of febrile neutropenia. *Infection* 44(2), 175-186.

Schaible AM, Filosa R, Krauth V, Temml V, Pace S, Garscha U, Liening S, Weinigel C, Rummler S, **Schieferdecker S**, Nett M, Peduto A, Collarile S, Scuotto M, Roviezzo F, Spaziano G, de Rosa M, Stuppner H, Schuster D, D'Agostino B, Werz O (2016) The 5-lipoxygenase inhibitor RF-22c potently suppresses leukotriene biosynthesis in cellulo and blocks bronchoconstriction and inflammation in vivo. *Biochem Pharmacol* 112, 60-71.

Sun Y, Meng Z, Chen P, Zhang D, **Baunach M**, **Hertweck C**, Li A (2016) A concise total synthesis of sespenine, a structurally unusual indole terpenoid from *Streptomyces*. *Org Chem Front* 3, 368-374.

Ueberschaar N, **Heine D**, **Hertweck C** (2016) Zinc(II)-assisted aryl-Finkelstein-reaction for the synthesis of aryl iodides. *Synlett* 27, 1794-1797.

Ueberschaar N, **Meyer F**, Dahse HM, **Hertweck C** (2016) Bipiperidine conjugates as soluble sugar surrogates in DNA-intercalating antiproliferative polyketides. *Chem Commun (Camb)* 52(27), 4894-4897.

Walther E, **Boldt S**, Kage H, Lauterbach T, Martin K, Roth M, **Hertweck C**, Sauerbrei A, Schmidtke M, Nett M (2016) Zincophorin – biosynthesis in *Streptomyces griseus* and antibiotic properties. GMS *Infect Dis* 4, doc08.

Wick J, **Heine D**, Lackner G, Misiek M, Tauber J, Jagusch H, **Hertweck C**, Hoffmeister D (2016) A fivefold parallelized biosynthetic process secures chlorination of *Armillaria mellea* (honey mushroom) toxins. *Appl Environ Microbiol* 82, 1196-1204.

Aiyar P, Schaeme D, **García-Altares M**, Carrasco Flores D, Dathe H, **Hertweck C**, Sasso S, Mittag M (2017) Antagonistic bacteria disrupt calcium homeostasis and immobilize algal cells. *Nat Commun* 8(1), 1756.

Baldeweg F, Kage H, **Schieferdecker S**, Allen C, Hoffmeister D, Nett M (2017) Structure of ralsolamycin, the inter-kingdom morphogen of the crop plant pathogen *Ralstonia solanacearum* GMI1000. *Org Lett* 19, 4868-4871.

Brandt P, **García-Altares M**, Nett M, **Hertweck C**, Hoffmeister D (2017) Induced chemical defense of a mushroom by a dou-

ble-bond-shifting polyene synthase. *Angew Chem Int Ed* 56(21), 5937-5941.

Flórez LV, **Scherlach K**, Gaube P, **Ross C**, Sitte E, Hermes C, Rodrigues A, **Hertweck C**, Kaltenpoth M (2017) Antibiotic-producing symbionts dynamically transition between plant pathogenicity and insect-defensive mutualism. *Nat Commun* 8, 15172.

Guljamow A, Kreische M, **Ishida K**, Liaimer A, Altermark B, Bähr L, **Hertweck C**, Ehwald R, Dittmann E (2017) High-density cultivation of terrestrial Nostoc strains leads to reprogramming of secondary metabolome. *Appl Environ Microbiol* 83(23), e01510-17.

Kloss F, Krchnak V, Krchnakova A, **Schieferdecker S**, Dreisbach J, Krone V, Möllmann U, Hoelscher M, Miller MJ (2017) *In vivo* dearomatization of the potent antituberculosis agent BTZ043 via Meisenheimer complex formation. *Angew Chem Int Ed* 56(8), 2187-2191.

Kugel S, **Baunach M**, Baer P, **Ishida-Ito M**, **Sundaram S**, **Xu Z**, Groll M, **Hertweck C** (2017) Cryptic indole hydroxylation by a non-canonical terpenoid cyclase parallels bacterial xenobiotic detoxification. *Nat Commun* 8, 15804.

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Shao Y, Chen B, Sun C, **Ishida K**, **Hertweck C**, Boland W (2017) Symbiont-derived antimicrobials contribute to the control of the lepidopteran gut microbiota. *Cell Chem Biol* 24(1), 66-75.

Valiante V, Mattern DJ, Schüffler A, Horn F, Walther G, **Scherlach K**, Petzke L, Dickhaut J, Guthke R, **Hertweck C**, Nett M, Thines E, Brakhage AA (2017) Discovery of an extended austinoid biosynthetic pathway in *Aspergillus calidoustus*. *ACS Chem Biol* 12(5), 1227-1234.

Department Bio Pilot Plant

Chankhamjon P, Tsunematsu Y, Ishida-Ito M, Sasa Y, Meyer F, Boettger-Schmidt D, Urbansky B, **Menzel KD**, Scherlach K, Watanabe K, Hertweck C (2016) Regioselective dichlorination of a non-activated aliphatic carbon atom and phenolic bismethylation by a multifunctional fungal flavoenzyme. *Angew Chem Int Ed* 55(39), 11955-11959.

Funk J, Schaarschmidt B, Slesiona S, Hallström T, **Horn U**, Brock M (2016) The glycolytic enzyme enolase represents a plasminogen-binding protein on the surface of a wide variety of medically important fungal species. *Int J Med Microbiol* 306(1), 59-68.

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Heine D, Sundaram S, Beudert M, **Martin K**, Hertweck C (2016) A widespread bacterial phenazine forms conjugates with biogenic thiols and crosslinks proteins. *Chem Sci* 7, 4848-4855.

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Kämpfer P, Glaeser SP, Kloepper JW, Hu CH, McInroy JA, **Martin K**, Busse HJ (2016) *Isoptericola cucumis* sp. nov., isolated from the root tissue of cucumber (*Cucumis sativus*). *Int J Syst Evol Microbiol* 66, 2784-2788.

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Kollmer M, Meinhardt K, Haupt C, Liberta F, Wulff M, Linder J, Handl L, Heinrich L, Loos C, Schmidt M, Syrovets T, Simmet T, Westermark P, Westermark GT, **Horn U**, Schmidt V, Walther P, Fändrich M (2016) Electron tomography reveals the fibril structure and lipid interactions in amyloid deposits. *Proc Natl Acad Sci U S A* 113(20), 5604-5609.

Lüdecke C, **Roth M**, Yu W, **Horn U**, Bossert J, Jandt KD (2016) Nanorough titanium surfaces reduce adhesion of *Escherichia coli* and *Staphylococcus aureus* via nano adhesion points. *Colloids and Surfaces B - Biointerfaces* 145, 617-625.

Walther E, Boldt S, Kage H, Lauterbach T, **Martin K**, **Roth M**, Hertweck C, Sauerbrei A, Schmidtke M, Nett M (2016) Zincophorin – biosynthesis in *Streptomyces griseus* and antibiotic properties. *GMS Infect Dis* 4, doc08.

Wulff M, Baumann M, Thümmler A, Yadav JK, Heinrich L, **Knüpfer U**, Schlenzig D, Schierhorn A, Rahfeld JU, **Horn U**, Balbach J, Demuth HU, Fändrich M (2016) Enhanced fibril fragmentation of N-terminally truncated and pyroglutamyl-modified Aβ peptides. *Angew Chem Int Ed* 55(16), 5081-5084.

Guo H, Benndorf R, Leichnitz D, Klassen JL, Vollmers J, Görls H, **Steinacker M**, Weigel C, Dahse HM, Kaster AK, de Beer ZW, Poulsen M, Beemelmanns C (2017) Isolation, biosynthesis and chemical modifications of rubterolones A–F, rare tropolone alkaloids from *Actinomadura* sp. 5-2. *Chem Eur J* 23(39), 9338-9345.

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Department Infection Biology

Buhlmann D, **Eberhardt HU**, Medyukhina A, Prodinger WM, Figge MT, **Zipfel PF**, **Skerka C** (2016) FHR3 blocks C3d-mediated coactivation of human B cells. *J Immunol* 197(2), 620-629.

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Guo H, Kreuzenbeck NB, Otani S, Garcia-Altares M, **Dahse HM**, Weigel C, Aanen DK, Hertweck C, Poulsen M, Beemelmanns C (2016) Pseudoxylallemycins A-F, cyclic tetrapeptides with rare allenyl modifications isolated from *Pseudoxylaria* sp. X802: A competitor of fungus-growing termite cultivars. *Org Lett* 18, 3338-3341.

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Associated Group Pharmaceutical Microbiology

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Kniemeyer, Olaf
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Frontiers in Microbiology
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Journal of Basic Microbiology
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Frontiers in Genetics

Zipfel, Peter F.
Frontiers in Innate Immunity
Molecular Immunology

LECTURES AT THE HKI **KOLLOQUIEN AM HKI**

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Panagiotou, Gianni
School of Biological Sciences, The University of Hong Kong, Hong Kong
Microbiome Systems Biology: The Interplay between Genome, Metagenome and Exposome
12.01.2016

Mitchell, Douglas A.
University of Illinois at Urbana-Champaign, USA
Genomics-Enabled Natural Products Discovery
16.03.2016

Kaufmann, Stefan H. E.
Max Planck Institute for Infection Biology, Berlin, Germany
Immune Response to Tuberculosis: How to Control the Most Successful Pathogen on Earth
12.05.2016

Agler-Rosenbaum, Miriam
RWTH Aachen, Germany
Exploring and utilizing phenazine-based anodic electron discharge in pure and co-culture microbial bioelectrochemical systems
05.07.2016

Meier, Matthias
Albert-Ludwigs-Universität Freiburg, Germany
Microfluidic and Biological Engineering
05.07.2016

Bramkamp, Marc
Ludwig-Maximilians-Universität München, Germany
Making antibiotic action visible: use of microfluidics and advanced imaging to address targets of antimicrobial compounds
05.07.2016

Schiller, Stefan M.
Albert-Ludwigs-Universität Freiburg, Germany
From the Modular Expansion of Cellular Functions to New Drug Platforms
05.07.2016

Kalkum, Markus
Beckman Research Institute, Duarte, USA
Vaccines and novel Diagnostics for Invasive Fungal Infections
07.07.2016

Ferretti, Joseph J.
University of Oklahoma, USA
Comparative genomics as a tool for understanding the evolution of diseases caused by the pathogen Streptococcus pyogenes
HKI Colloquium in collaboration with the "Akademie gemeinnütziger Wissenschaften zu Erfurt"
02.09.2016

Brunner-Weinzierl, Monika
University of Magdeburg, Germany
T cells as gatekeepers of tolerance and immunity against microbes
04.10.2016

2017

Rohr, Jürgen
College of Pharmacy, University of Kentucky, UK
Post-PKS Tailoring Enzyme Complexes and their Impact on Drug Discovery
27.02.2017

Tan, Zhongping
University of Colorado Boulder, USA
Using Chemical Biology to Understand and Apply Protein O-Glycosylation
26.04.2017

Kolev, Martin
MRC Centre for Transplantation, King's College London, UK
Intracellular complement links metabolism with T cell immunity: past, present and future
09.05.2017

Gutsmann, Thomas
Research Center Borstel, Leibniz Lung Center, Borstel, Germany
Microbes and Humans: a Battle Between Membranes and Pores
10.05.201

Hörnke, Maria
Albert-Ludwigs-Universität Freiburg, Germany
Lipid selectivity in antimicrobial activity
10.07.2017

Krause, André
Jena Bioscience, Jena, Germany
Click Chemistry - Expanding the Scope of Nucleic Acid Labeling
24.10.2017

Mzinza, David
Medizinische Hochschule Hannover, Germany
Induction of bronchus-associated lymphoid tissue by *E. coli*, and establishment of a method for its analysis in whole mouse lung lobes
16.11.2017

Diefenbach, Andreas
Institut für Mikrobiologie der Charité, Universitätsmedizin Berlin, Germany
How the microbiota instructs the epigenetic and metabolic groundstate of the immune system
21.11.2017

Kline, Kimberly Ann
Nanyang Technological University, Singapore
Mechanisms of enterococcal infection and persistence in the host
11.12.2017

MEETINGS, WORKSHOPS, SYMPOSIA
WISSENSCHAFTLICHE VERANSTALTUNGEN

2016

Irseer Naturstofftage der DECHEMA
Hertweck, Christian
Irsee, Germany

FEBS Practical Course: State-of-the-art infection models to study molecular mechanisms of human fungal infections
Jacobsen, Ilse D.; Hube, Bernhard
Jena, Germany

Leibniz-Wirkstofftage 2016
Brakhage, Axel A.; Kloß, Florian; Scherlach, Kristin
Jena, Germany

2nd FunComPath Meeting
Graf, Katja; Hube, Bernhard
Gothenborg, Sweden

Leopoldina Symposium: Sepsis – The challenges of science, politics and society
Brakhage, Axel
Jena, Germany

VAAM Annual Meeting
Brakahge, Axel; Figge, Marc Thilo; Hoffmeister, Dirk; Valiante, Vito; Voigt, Kerstin
Jena, Germany

ICSB Satellite Workshop Systems Biology of Transcription Regulation
Shelest, Ekaterina
Barcelona, Spain

Joint Meeting ILRS Jena and RTG 1870 University of Greifswald
Vogler, Christine; Zipfel, Peter
Lutherstadt Wittenberg, Germany

Symposium "From Images to Models: The role of Image Data in Systems Biology"
Svensson, Carl-Magnus
Nottingham, UK

European Conference on Computational Biology
Figge, Marc Thilo
The Hague, Netherlands

3rd International Workshop on Image-based Systems Biology
Figge, Marc Thilo
Jena, Germany

Nachwuchswissenschaftler-Symposium Bioorganische Chemie
Beemelmanns, Christine; Stallforth, Pierre
Jena, Germany

International Study Group for Systems Biology
Figge, Marc Thilo
Jena, Germany

From biofactories to cell-free systems: Novel ways of BioProcess design; Jahreskongress des Strategieprozesses „Nächste Generation biotechnologischer Verfahren – Biotechnologie 2020+"
Brakhage, Axel; Valiante, Vito
Jena, Germany

Industry Contact Forum (Joint PhD meeting of CRC/Transregio 124 FungiNet and InfectControl 2020)
Brakhage, Axel
Jena, Germany

2017

Irseer Naturstofftage der DECHEMA
Hertweck, Christian
Irsee, Germany

International Conference on Microbial Communication for Young Scientists
Cseresnyés, Zoltán; Conrad, Theresia; Ferling, Iuliia; Figge, Marc Thilo
Jena, Germany

3rd FunComPath Meeting
Graf, Katja; Hube, Bernhard
Madrid, Spain

Symposium: BioSynthetic Strategies Towards New Antimicrobial Natural Products
Beemelmanns, Christine
Jena, Germany

2nd Central German Meeting on Bioinformatics
König, Rainer
Leipzig, Germany

Strategy Conference InfectControl 2020
Brakhage, Axel
Jena, Germany

Marie Sklodowska-Curie ITN OPATHY Midterm Meeting
Hube, Bernhard; Pekmezovic, Marina
Jena, Germany

Annual Meeting of the DMykG
Kurzai, Oliver
Münster, Germany

Invasive Mycoses in Haematological Malignancies (IMIHM) XI
Kurzai, Oliver
Würzburg, Germany

4th International Symposium on Systems Biology of Microbial Infection
Figge, Marc Thilo; Panagiotou, Gianni
Jena, Germany

VAAM Meeting Molecular Biology of Fungi
Brakhage, Axel; Hillmann, Falk; Valiante, Vito
Jena, Germany

World Health Summit 2017, WS 19 – Sepsis and Infections in the 21ST Century
Hube, Bernhard
Berlin, Germany

Life meets Light – First Scientific Conference of the Leibniz ScienceCampus InfectoOptics
Brakhage, Axel
Jena, Germany

Meeting of the VAAM Special Group "Molecular Biology of Fungi"
Brakhage, Axel; Hillmann, Falk; Valiante, Vito
Jena, Germany

SCIENTIFIC AWARDS
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Photo Award
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Förster, Toni
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Ishida, Keishi
Leibniz Drug of the Year 2016
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Kasper, Lydia
medac Research Award
medac GmbH, Wedel

Klapper, Martin
medac Research Award
medac GmbH, Wedel

Kniemeyer, Olaf
medac Research Award
medac GmbH, Wedel

Krüger, Thomas
medac Research Award
medac GmbH, Wedel

Kugel, Susann
medac Research Award
medac GmbH, Wedel

Luo, Ting
medac Research Award
medac GmbH, Wedel

Mahler, Lisa
Poster Award
EMBL Microfluidics Conference

Mogavero, Selene
medac Research Award
medac GmbH, Wedel

Mogavero, Selene
Publication Award of the DMykG Foundation Stiftung der Deutschsprachigen Mykologischen Gesellschaft e.V. (DMykG)

Rudnick, Ramona
Poster Award
8. Jahrestagung der Deutschen Gesellschaft für Nephrologie (DGfN)

Shabuer, Gulimila
Leibniz Drug of the Year 2016
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Skrahina, Volha
E-Poster Award
Deutsche Gesellschaft für Hygiene und Mikrobiologie e.V. (DGHM)

Stallforth, Pierre
medac Research Award
medac GmbH, Wedel

Willing, Karsten
medac Research Award
medac GmbH, Wedel

Wilson, Duncan
medac Research Award
medac GmbH, Wedel

Wilson, Duncan
Publication Award of the DMykG Foundation Stiftung der Deutschsprachigen Mykologischen Gesellschaft e.V. (DMykG)

2017

Barber, Amelia
ECMM Young Investigator Travel Award
8th Trends in Medical Mycology (TIMM) Congress

Baunach, Martin
Poster Award
Irseer Naturstofftage

Brandt, Philip
medac Research Award
medac GmbH, Wedel

Eckhardt, Dorothee
Leibniz Trainee Award
Leibniz Association

Eckhardt, Dorothee
Weiterbildungsstipendium
IHK Ostthüringen

Ferling, Iuliia
Poster Award
International Dictyostelium Conference – DICTY 2017

Garcia Altares-Perez, Maria
medac Research Award
medac GmbH, Wedel

Gore, Sagar
Poster Award
IEEE International Conference on Computational Intelligence in Bioinformatics and Computational Biology

Halder, Luke D.
Poster Award
16th European Meeting on Complement in Human Disease

Hörhold, Franziska
Poster Award
Weimar Sepsis Update 2017

Hube, Bernhard
Leibniz Drug of the Year 2017
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Ishida-Ito, Mie
medac Research Award
medac GmbH, Wedel

Klapper, Martin
Talk Award
ILRS Symposium 2017

Kloß, Florian
medac Research Award
medac GmbH, Wedel

Lange, Antonia
Poster Award
Deutschsprachige Mykologische Gesellschaft e.V. (DMykG)

Mahler, Lisa
Poster Award
Gordon Research Conference Physics and Chemistry of Microfluidics

Mogavero, Selene
Leibniz Drug of the Year 2017
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Netzker, Tina
Poster Award
18th International Symposium on the Biology of Actinomycetes

Panagiotou, Gianni
Research Output Prize 2017
Faculty of Science, The University of Hong Kong

Polke, Melanie
Scientific Award of the DMykG Foundation Stiftung der Deutschsprachigen Mykologischen Gesellschaft e.V. (DMykG)

Polke, Melanie
Poster Award
Human Fungal Pathogens 2017

Scheven, Mareike
Hans Rieth Poster Award
Deutschsprachige Mykologische Gesellschaft e.V. (DMykG)

Scheven, Mareike
Poster Award
1st FeSBioNET Training School

Scheven, Mareike
Talk Award
ILRS Symposium 2019

Schieferdecker, Sebastian
medac Research Award
medac GmbH, Wedel

Shekhova, Elena
Poster Award
International Conference on Microbial Communication for Young Scientists – MiCom 2017

Skrahina, Volha
Best Elevator Presentation
British Society for Medical Microbiology

Stallforth, Pierre
Talk Award
nternational Dictyostelium Conference – DICTY 2017

Sundaram, Srividhya
medac Research Award
medac GmbH, Wedel

Mahler, Lisa
Poster Award
18th International Symposium on the Biology of Actinomycetes

Tille, Alexander
Poster Award
ILRS Symposium 2017

Wilson, Duncan
Leibniz Drug of the Year 2017
Leibniz Research Alliance Bioactive Compounds and Biotechnology

CALLS FOR APPOINTMENTS **RUFE**

Agler-Rosenbaum, Miriam
Call for a W3 Professorship in Synthetic Biotechnology at Friedrich Schiller University Jena (2017)

Ruf auf eine W3-Professur für Synthetische Biotechnologie an die Friedrich-Schiller-Universität Jena (2017)

Panagiotou, Gianni (Hongkong)
Call for a Honorary Associate Professorship at The University of Hong Kong (2017)

Ruf auf eine Honorarprofessur an der Universität Hongkong (2017)

Kurzai, Oliver
Call for a W3 professorship in Medical Microbiology and Mycology at Julius Maximilians University Würzburg (2017)

Ruf auf eine W3-Professur für Medizinische Mikrobiologie und Mykologie an die Julius-Maximilians-Universität Würzburg (2017)

GRADUATIONS **PROMOTIONEN**

2016

Bohnert, Markus
Melleolid-Antibiotika aus *Armillaria mellea*: Evaluation der biologischen Aktivität
Friedrich-Schiller-Universität Jena

Brandes, Susanne
Automated analysis of dynamic properties in biological systems from image data
Friedrich-Schiller-Universität Jena

Dieckmann, Anna
Systems biological analysis of signal transduction in telomere length maintenance
Universität Heidelberg

Dix, Andreas
Analysis of genome-wide expression data to detect biomarkers for infections with *Aspergillus fumigatus* and *Candida albicans*
Friedrich-Schiller-Universität Jena

Duggan, Séana
The interaction of *Candida glabrata* with human neutrophils
Friedrich-Schiller-Universität Jena

Essig, Fabian
Analyse der Aktivierung des angeborenen Immunsystems durch *Candida* spp. mittels Lebendzellmikroskopie
Friedrich-Schiller-Universität Jena

Fischer, Juliane
Chromatin remodelling during fungal-bacterial interaction
Friedrich-Schiller-Universität Jena

Föge, Martin
G-Protein-gekoppelte Rezeptoren in *Aspergillus fumigatus*
Friedrich-Schiller-Universität Jena

Heine, Daniel
Charakterisierung ungewöhnlicher Polyketidsynthasen für die Einführung von Kettenverzweigungen und Entdeckung neuer Antibiotika aus seltenen Actinomycten
Friedrich-Schiller-Universität Jena

Höfs, Sarah
Identification of Candidalysin – a *Candida albicans* peptide toxin involved in epithelial damage
Friedrich-Schiller-Universität Jena

Kröber, Antje
Funktionelle Charakterisierung von Transkriptionsregulatoren im humanpathogenen Dermatophyten *Arthroderma benhamiae*
Friedrich-Schiller-Universität Jena

Lindner, Susanne
Autoantikörper gegen die Bestandteile der C3-Konvertase bei Membranoproliferativer Glomerulonephritis
Friedrich-Schiller-Universität Jena

Luo, Ting
Proteomic analysis of the *Candida albicans* secretome and its antigenic properties in the human host
Friedrich-Schiller-Universität Jena

Mohebbi, Sara
Hyperspectral imaging using intracellular spies: quantitative real-time measurement of intracelluar parameters *in vivo* during host-pathogen interaction
Friedrich-Schiller-Universität Jena

Netzker, Tina
Genetische Modifikation von *Streptomyces iranensis* und Charakterisierung von dessen Interaktion mit Pilzen
Friedrich-Schiller-Universität Jena

Park, Hea Reung
The intraphagocytic long-term survival of the mucormycotic agent *Lichtheimia corymbifera*
Friedrich-Schiller-Universität Jena

Pollmächer, Johannes
Individual-based modeling and predictive simulation of fungal infection dynamics
Friedrich-Schiller-Universität Jena

Schwartze, Volker
Pathogenomic analysis of Lichtheimia species as a model for basal human pathogenes of the order Mucorales
Friedrich-Schiller-Universität Jena

Seccareccia, Ivana
Unraveling predator-prey interactions between bacteria
Friedrich-Schiller-Universität Jena

2017

Ackermann, Susanne
Die Rolle von Apolipoprotein E bei der humanen Immunreaktion
Friedrich-Schiller-Universität Jena

Baunach, Martin
Aufklärung der Biosynthese von Sekundärmetaboliten aus Mangroven-Endophyten
Friedrich-Schiller-Universität Jena

Böttcher, Bettina
Identifizierung pathogenitätsrelevanter Gene in *Candida albicans* und *Candida dubliniensis*
Friedrich-Schiller-Universität Jena

Braga, Daniel
Investigating the substrate specificity of multimodular enzymes of higher fungi and a predatory bacterium
Friedrich-Schiller-Universität Jena

Brandenburger, Eileen
Untersuchung der Substratspezifitäten von Adenylierungsdomänen aus Ascomyceten und Basidiomyceten
Friedrich-Schiller-Universität Jena

Buhlmann, Denise
Die Rolle des Komplementrezeptors 2 (CR2/CD21) bei der Regulation der innaten und adaptiven Immunität
Friedrich-Schiller-Universität Jena

Dornblut, Katharina
Pathogene und mutualistische Bakterien-Pilz-Interaktionen – Genombasierte Analyse von pilzassoziierten Bakterien als Naturstoffproduzenten und von Virulenzfaktoren in Champignonkrankheiten
Friedrich-Schiller-Universität Jena

Gerwien, Franziska
Iron acquisition and regulation in the fungal pathogen *Candida glabrata*
Friedrich-Schiller-Universität Jena

Grätig, Cornelia
Unraveling predator-prey interactions between bacteria
Friedrich-Schiller-Universität Jena

Hoffmann, Bianca
Automated quantification of experimental arthritis based on *in vivo* PET/CT imaging
Friedrich-Schiller-Universität Jena

Huyke, Johanna
Molecular and phenotypic characterization of *Candida albicans* bloodstream isolates from a German university hospital
Friedrich-Schiller-Universität Jena

Kraibooj, Kaswara
Unraveling predator-prey interactions between bacteria
Friedrich-Schiller-Universität Jena

Lehnert, Teresa
Predictive modelling and quantitative simulation of immune responses to human-pathogenic fungi
Friedrich-Schiller-Universität Jena

Linden, Justus
Immunevasion of the human pathogenic yeast *Candida albicans*
Friedrich-Schiller-Universität Jena

Mattern, Derek
Metabolic engineering and bioprospecting of natural products in *Aspergillus* species
Friedrich-Schiller-Universität Jena

Meckel, Katharina
Die Effektivität der empirischen antibiotischen Therapie der febrilen Neutropenie – retrospektiver Vergleich der zwischen 2012 und 2014 am Universitätsklinikum Jena durchgeführten Therapien
Friedrich-Schiller-Universität Jena

Meinel, Christian
Streptococcus pneumoniae von Patienten mit hämolytisch-urämischem Syndrom schädigen Endothelzellen durch aktiviertes Plasmin und inhibieren das Komplementsystem
Friedrich-Schiller-Universität Jena

Meyer, Florian
Synthetische Modifizierung antifungal und zytostatisch wirksamer Naturstoffe
Friedrich-Schiller-Universität Jena

Ni, Yueqiong
Integrative analysis of the human genome, metagenome and exposome
University of Hong Kong

Pohlers, Susann
CO_2 Adaptation in *Candida glabrata* und ihre Rolle in der Pathogen-Wirt-Interaktion
Friedrich-Schiller-Universität Jena

Polke, Melanie
The role of the *Candida albicans* EED1 in quorum sensing, morphogenesis and virulence
Friedrich-Schiller-Universität Jena

Schmidt, Hella
Melanin-dependent modification of phagolysosomal processing of conidia of the human pathogenic fungus *Aspergillus fumigatus* in macrophages
Friedrich-Schiller-Universität Jena

Schuwirth, Maria
Häufigkeit und Verlauf invasiver Pilzinfektionen bei neutropenischen Patienten unter besonderer Berücksichtigung von Umweltfaktoren, antimykotischer Prophylaxe und Grunderkrankung – eine retrospektive Analyse
Friedrich-Schiller-Universität Jena

Shekhova, Elena
Adaption of the fungal pathogen *Aspergillus fumigatus* to stress environments by modulating cellular redox signaling
Friedrich-Schiller-Universität Jena

Sundaram, Srividhya
Biochemical of non-canonical branching module of the rhizoxin polyketide synthase
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Wolf, Thomas
Entwicklung bioinformatischer Methoden zur Vorhersage von Sekundärmetabolit-Gen-Clustern in Pilzen
Friedrich-Schiller-Universität Jena

Zhao, Fei
C3 glomerulopathy associated antibodies deregulate complement on different levels
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BACHELOR / MASTER / DIPLOMA THESES
BACHELOR- / MASTER- / DIPLOMARBEITEN

2016

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Auge, Isabell
Charakterisierung der Komplementregulation auf retinalen Pigmentepithelzellen
Friedrich-Schiller-Universität Jena

Böttcher, Sarah
Die Rolle des Milieus und der *Candida*-Spezies auf die Aktivität von NK-Zellen
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Ehle, Charlotte
Heterologe Expression eines polyketidsynthasegens aus *Clostridium acetobutylicum*
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Eifert, Theresa
Interaktion von Leukozyten mit *Aspergillus fumigatus* Deletionsmutanten ΔcspA und Δgel2 – Vergleich von Phagozytose und Oberflächen-Antigen Expression
Friedrich-Schiller-Universität Jena

Faber, Marius
Charakterisierung und Evaluation von Ganzzell-Biosensoren zur Detektion antibiotikavermittelter Stressreaktionen
Ernst-Abbe-Hochschule Jena

Heinze, Beatrix
Lassopeptide aus dem endofungalen Bakterium *Burholderia rhizoxinica*
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Kröll, Sandra
On-line Dehydratisierung von nicht-ribosomalen Peptidendurch eine multifunktionale Kondensationsdomäne
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Meyer, Daria
FLT3-ITD dependent aberrations of gene expressin in AML patients
Friedrich-Schiller-Universität Jena

Schmidt, Saskia
Einfluss von Konidienkomponenten von *Aspergillus fumigatus* auf die Immunabwehr durch Makrophagen
Friedrich-Schiller-Universität Jena

Unger, Lucas
Suppressive Wirkung des *Phellinus pachyphloeus*-Extraktes auf humane HL-60-Leukämiezellen
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MASTER

Aly, Mahmoud
Interaction of human neutrophils with *Candida glabrata* HSP mutants
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Bredy, Florian
Heterologe Expression eines kryptischen Typ-II-PKS-Genclusters des anaeroben Bakteriums *Dendrosporobacter quercicolus* in *Escherischia coli*
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Burks, Thomas
Study towards amoebal polyketide biosynthesis
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Collatz, Maximilian
Analyzing alternative splicing and gene expression of neuroblastoma
Friedrich-Schiller-Universität Jena

Daum, Elena
Functional characterization of complement factor H related protein 2
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Dörschmann, Phillipp
Selektion und Charakterisierung von cameliden Antikörpern für die Diagnostik von Tuberkuloseinfektionen
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Dose, Benjamin
Investigating the exchange or shift of the thioesterease domain in the rhizoxin polyketide pathway of *Burkholderia rhizoxinica*
Friedrich-Schiller-Universität Jena

Feige, Anja
Charakterisierung und Weiterentwicklung eines *Escherichia coli*-Ganz-Zell-Assays zur Detektion antimikrobieller Wirkstoffe
Ernst-Abbe-Hochschule Jena

Förster, Birthe
Isolation and characterization of novel pleurotin derivatives from *Hohenbuehelia* spp.
Friedrich-Schiller-Universität Jena

Fricke, Janis
Heterologe Produktion und biochemische Charakterisierung von Prenyltransferasen und Polyketidsynthasen aus Basidiomyceten
Friedrich-Schiller-Universität Jena

Garbe, Enrico
Characterization of the *Candida albicans* ECE1 promoter
Friedrich-Schiller-Universität Jena

Gerber, Silvia
Genome-wide network inference for *Aspergillus fumigatus*
Friedrich-Schiller-Universität Jena

Greßler, Elisabeth
Die Rolle von *Candida albicans* ECE1 und EED1 für die Kolonisierung des und Dissiminierung aus dem murinen Gastrointestinaltrakt
Friedrich-Schiller-Universität Jena

Hermes, Cornelia
Untersuchung der Sekundärmetabolit-Produktion von *Burkholderia gladioli* in spezifischer Interaktion mit Pilzen und Insekten
Friedrich-Schiller-Universität Jena

Herzog, Susann
Interaction of human neutrophils with *Candida glabrata* deletion mutants
Friedrich-Schiller-Universität Jena

Hidalgo Vico, Susana
Strategies of *Candida albicans* to evade the complement mediated attack by human monocytes
Friedrich-Schiller-Universität Jena

Khan, Faisal
Comparative study of coding DNA sequences in *Chlamydia abortus*, *Chlamydia psittaci* and *Waddis chondrophila* including transcription start sites and ncRNA prediction in *C. abortus*
Friedrich-Schiller-Universität Jena

Köhler, Sarah
Candida albicans' pH-regulated antigen binds the immune regulator MCP
Friedrich-Schiller-Universität Jena

Krespach, Mario
Generierung und Charakterisierung von *Streptomyces iranensis* Deletionsmutanten
Friedrich-Schiller-Universität Jena

Kreuzenbeck, Nina
Chemical analysis of the fungal cultivar *Termitomyces* sp.
Friedrich-Schiller-Universität Jena

Mielke, Karolin
Phänotypische Charakterisierung infektionsassoziierter Gene in *Candida glabrata*
Friedrich-Schiller-Universität Jena

Mura-Mészáros, Anna
Type III secreted proteins of Chlamydiae and their interaction with host proteins
Friedrich-Schiller-Universität Jena

Nessel, Diana
Aktivierung und Interaktion von humanen Thrombozyten mit Neutrophilen Granulozyten während einer *Candida*-Infektion
Friedrich-Schiller-Universität Jena

Nold, Isabell
Generierung und Charakterisierung eines *E. coli*-Stammes zur induzierbaren genomischen Expression von mCherry als Basis eines Ganzzell-Assays für die Detektion antimikrobieller Wirkstoffe
Ernst-Abbe-Hochschule Jena

Ponnaganti, Neeharika
Conservation of regulatory patterns in fungal gene clusters
Hochschule Furtwangen

Praußе, Maria
Optimization of parameter estimation in virtual infection models for *Candida albicans*
Friedrich-Schiller-Universität Jena

Rothenburger, Linda
Interaktion des humanen Komplementproteins CFHR5 mit Erregerproteinen von *Streptococcus pneumoniae*
Friedrich-Schiller-Universität Jena

Safyan, Abu
Identification and characterization of novel factors crucial for iron homeostasis in *Candida glabrata*
Friedrich-Schiller-Universität Jena

Schanbacher, Franziska
Antimikrobielle Naturstoffe aus räuberischen Bakterien
Friedrich-Schiller-Universität Jena

Schmidt, Franziska
Intracellular processing of *Aspergillus fumigatus* conidia with macrophages and the role of lipid rafts
Friedrich-Schiller-Universität Jena

Sommerwerk, Elisabeth
Geochemical analysis of fungus-growing termite mounts
Friedrich-Schiller-Universität Jena

Stephan, Philipp
Chemical analysis of the fungal cultivar antagonist *Pseudoxylaria* X802 sp.
Friedrich-Schiller-Universität Jena

Wein, Philipp
Die Rolle der Sekretionssysteme in der Infektion des Champignons durch *Janthinobacterium agaricidamnosum*
Friedrich-Schiller-Universität Jena

Wittig, Franziska
Secondary *Candida albicans* yeast cells differ from their primary counterparts in cell surface and host cell interaction
Friedrich-Schiller-Universität Jena

Wu, Tsung-Yen
Expression and subcellular localization studies on the peroxiredoxin-like protein AspF3 in *Asperillus fumigatus* during oxidative stress and macrophage interactions
Friedrich-Schiller-Universität Jena

2017

BACHELOR

Cai, Jing
Construction and expression analysis of a GFP-tagged copper transporter in the pathogenic yeast *Candida parapsilosis*
Friedrich-Schiller-Universität Jena

Cyranka, Leon
Charakterisierung der antimikrobiellen Aktivität von Candidalysinderivaten
Friedrich-Schiller-Universität Jena

Hildebrand, Felina
Naturstoffe der phytopathogenen Bakterien *Ralstonia solanacearum* und *Rhizobium radiobacter*
Friedrich-Schiller-Universität Jena

Kilar, Agata
Iron redistribution after *Candida albicans* infection in the murine kidney
Silesian University of Technology, Gliwice, Polen

Kröller, Sarah
Einfluss der Ergosterol-Biosynthese auf Quorum sensing in Candida albicans
Friedrich-Schiller-Universität Jena

Matthes, Julian
Charakterisierung der Bindung von humanen Serumproteinen an das Lipidperoxidationsprodukt Malondialdehyd-Acetaldehyd (MAA)
Friedrich-Schiller-Universität Jena

Schleich, Fabian-Alexander
Konstruktion und funktionelle Analyse der flavinbhängigen Halogenase AoiQ
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Shahda, Sophie
Untersuchung des putativen Sinapigladiosid-Biosynthese-Genclusters aus dem Endosymbionten *Burkholderia gladioli*
Friedrich-Schiller-Universität Jena

Unger, Sandra
Heterologe Expression eines Poyketid-synthase-Genclusters aus *Clostridium thermocellum* in *Escherichia coli*
Friedrich-Schiller-Universität Jena

Wohlsperger, Leopold
Entwicklung einer Methode zur Proteinquantifizierung in mikrofluidischen Tropfen
Friedrich-Schiller-Universität Jena

MASTER

Elshafee, Osama
Investigating the fitness role of the *Candida albicans* protein Ece1 using novel *in vitro* and *ex vivo* competition models
Friedrich-Schiller-Universität Jena

Fatah, Mahmoud A.
Role of complement factor H on extracellular DNA traps
Friedrich-Schiller-Universität Jena

Gonzalez Rojas, Katherine
The impact of the Aryl Hydrocarbon Receptor on the recognition of *Aspergillus fumigatus*
Friedrich-Schiller-Universität Jena

Gratz, Rena
Immunomodulatory properties of probiotic Lactobacilli in a commensal gut model
Friedrich-Schiller-Universität Jena

Hänsch, Veit
Mechanistische Untersuchungen zur licht-induzierten Synthese von Biarylen
Friedrich-Schiller-Universität Jena

Hanke, Jasmin
Funktionelle Charakterisierung von CFHR1
Friedrich-Schiller-Universität Jena

Hille, Fabrice
Interaction of *Candida glabrata* with macrophages – escape and impact on macrophage polarization
Friedrich-Schiller-Universität Jena

Keiff, Francois
Modulare Synthese eines natürlichen Lipodipeptides und dessen Derivaten und die Evaluierung ihrer Bioaktivität
Friedrich-Schiller-Universität Jena

Keßler, Sophie
Comparative metagenomic analysis of fungal diversity in *Penaeus monodon* from Indonesia
Friedrich-Schiller-Universität Jena

Knoll, Alisa
Isolation von Vakuolen und sequentielle Proteinextraktion aus *Papaver nudicaule* Blüten
Friedrich-Schiller-Universität Jena

Koleci, Naile
Enolase of *Aspergillus fumigatus* binds human Plasminogen and complement regulators
Friedrich-Schiller-Universität Jena

Landmann, Annemarie
The role of the *Candida albicans* kinase Ssn3 in rugulation of filamentation
Friedrich-Schiller-Universität Jena

Lange, Antonia
Assessment of azole resistance in environmentally-isolated *Aspergillus fumigatus* and the prevalence of mismatch repair mutations in multi-drug resistant strains of Candida glabrata
Friedrich-Schiller-Universität Jena

Leonhardt, Anne
Selektion von VHH-Domänen aus einer cameliden Antikörperbibliothek für den Einsatz in der Tuberkulosediagnostik
Ernst-Abbe-Hochschule Jena

Madaan, Vidushi
Tef1α of *Candida albicans* modulates B cell signalling and drives B cells to a regulatory phenotype
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Malladi, Ananya
Heterologous expression of the *Dictyostelium discoideum* Phosphopantetheinyltransferase gene in *Aspergillus fumigatus*
Friedrich-Schiller-Universität Jena

Matos de Opitz, Cruz Leila
Characterization of virulence determinants of *Aspergillus fumigatus*
Friedrich-Schiller-Universität Jena

Müller, Andrea
Untersuchungen zur Verteilung und Biosynthese von phenolischen Glycosiden in Salicaceae
Friedrich-Schiller-Universität Jena

Müller, Charlotte
Comparative microbiome analysis of *Perna viridis* (Indonesia) and *Perna canaliculus* (New Zealand)
Friedrich-Schiller-Universität Jena

Nguinkal, Julien
Biomarkers Prediction based on Time Course RNA-Seq Data
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Pflanze, Sebastian
Stereoselektiver Zugang zu gelabelten Sulfonolipiden als chemische Sonden zu Untersuchung mikrobiell-induzierter Morphogenese
Friedrich-Schiller-Universität Jena

Prantz, Anja
Recognition by and response of different epithelial cells to *Candida albicans* infection
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Reinhold, Annett
Untersuchung des Mykotoxinspektrums und Quantifizierung von Fumonisinen in Maismehl aus Malawi
Friedrich-Schiller-Universität Jena

Roos,Stefanie
Phänotypisierung und Proteomanalyse eines attenuierten Isolats des humanpathogenen Pilzes *Lichtheimia ramosa*
Friedrich-Schiller-Universität Jena

Schmidt, Alexander
Isolierung Und Identifizierung von neuartigen bioaktiven zyklischen Tetrapeptiden aus *Pseudoxylaria* sp. X802
Friedrich-Schiller-Universität Jena

Seelbinder, Bastian
Implementierung einer differentiellen RNA-Seq pipeline in R
Friedrich-Schiller-Universität Jena

Suhas Vasantha, Kumar Bhandari
Expression of genes encoding putative malonate carrier protein and malonyl-CoA synthetase (matB) in *Saccharomyces cerevisiae* to increase the malonyl-CoA production
Friedrich-Schiller-Universität Jena

Telagathoti, Anusha
Monitoring pH and apoptosis upon fungal infection of monocytes using hyperspectral imaging microscopy
Friedrich-Schiller-Universität Jena

Tischendorf, Ricardo
Produktbildung und Aufarbeitung von Netropsin aus *Streptomyces netropsis*
Technische Universität Braunschweig

Trottmann, Felix
Untersuchungen zur Biosynthese von Virulenz-assoziierten Natursstoffen aus *Burkholderia thailandensis*
Friedrich-Schiller-Universität Jena

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Leibniz Institute for Natural Product Research and Infection Biology
– Hans Knöll Institute –
Visiting address:
Beutenbergstraße 11a • 07745 Jena
Postal address:
Adolf-Reichwein-Straße 23 • 07745 Jena

+49 3641 532-1000
info@leibniz-hki.de

www.leibniz-hki.de

Editorial Board
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