LEIBNIZ-HKI

Leibniz-Institut
für Naturstoff-Forschung
und Infektionsbiologie
Hans-Knöll-Institut

RESEARCH REPORT 2019/2020

Leibniz Gemeinschaft

VORWORT

Liebe Leserinnen, liebe Leser,

„Neue Wege in der Prävention und Therapie von Krankheiten und im Umweltschutz“

auf die Jahre 2018 bis 2020 blicke ich mit äußerst positiven Gefühlen: Ich kann die Aufregung förmlich spüren, wenn ich mich an die Sommermonate 2018 zurückerinnere, in denen wir den Exzellenzcluster „Balance of the Microverse“ verteidigt haben. Gleichzeitig bin ich sehr dankbar, dass sich all die Aufregung und auch Anstrengungen gelohnt haben: Denn im September erhielten wir die erfreuliche Nachricht, dass Jena in der Exzellenzstrategie des Bundes und der Länder erfolgreich beteiligt ist. „Das ist der endgültige Durchbruch für Jena als ein international bedeutendes Wissenschaftszentrum“, sagte Thüringens Wissenschaftsminister Wolfgang Tiefensee damals und ich kann dem nur zustimmen. Das Leibniz-HKI hat einen wesentlichen Anteil am Erfolg des Exzellenzclusters. Nahezu alle unsere Gruppenleiterinnen und Gruppenleiter sind im neuen Netzwerk beteiligt und bringen ihre Forschungsideen zur Aufklärung der Funktion von mikrobiellen Gemeinschaften ein. Ich bin davon überzeugt, dass diese Forschung ganz neue Wege der Prävention und Therapie von Krankheiten und im Umweltschutz eröffnen wird.

„Neue Impulse in der Naturstoff-Forschung“

Gleich zwei Wissenschaftlerinnen des Leibniz-HKI setzten auf europäischer Ebene ein Zeichen:

Christine Beemelmanns überzeugte den Europäischen Forschungsrat mit ihrem Projekt MORPHEUS. Mit dem ERC Starting Grant in Höhe von 1,5 Millionen Euro wird sie in Zukunft untersuchen, wie Meeresbakterien die Entwicklung von Stachelpolypen steuern und sie mithilfe von natürlichen Antibiotika beschützen.

Miriam Rosenbaum setzte sich in dem internationalen Wettbewerb mit einem neuen Forschungsgebiet durch: der mikrobiellen Bioelektrochemie, für das sie einen ERC Consolidator Grant in Höhe von zwei Millionen Euro erhielt. Beide Projekte setzen neue Impulse in der Naturstoff-Forschung auf der Suche nach dringend benötigten Wirkstoffen für die Medizin. Ich gratuliere Christine Beemelmanns und Miriam Rosenbaum zu ihrem verdienten Erfolg.

Ein Höhepunkt der letzten Jahre war auch der Besuch des ERC-Präsidenten Prof. Jean-Pierre Bourguignon am Leibniz-HKI im November 2018. Es war uns eine Freude, ihm die Labore der ERC *Grantees* vorzustellen und mit ihm und weiteren Jenaer ERC *Grantees* über die europaweite Förderung und Vernetzung der Spitzenforschung zu diskutieren.

„Ansätze für neue Therapien gegen lebensgefährliche Pilzinfektionen“

Bei verdientem Erfolg denke ich sofort an zwei weitere Wissenschaftler: Mark Gresnigt und Matthew G. Blango zum Beispiel, die 2020 jeweils eine neue Nachwuchsgruppe am Leibniz-HKI etablierten. Es liegt in der Philosophie unseres Instituts, wissenschaftlichen Nachwuchs auszubilden und ihm gleichzeitig die Chance zu eröffnen, die eigene Karriere mit unabhängigen Projekten voranzutreiben.

Mit dem renommierten Emmy Noether-Programm unterstützt die Deutsche Forschungsgemeinschaft Mark Gresnigt beim Aufbau seiner Gruppe. Er wird mit seinem Team erforschen, wie sich das menschliche Immunsystem und pathogene Pilze gegenseitig wahrnehmen. Matthew G. Blango erhielt eine Förderung vom Bundesministerium für Bildung und For-

schung. Er und sein Team konzentrieren sich auf die Rolle von RNA bei invasiven Pilzinfektionen. Beide Nachwuchsgruppen werden wichtige Einblicke bringen, die Ansätze für neue Therapien gegen lebensgefährliche Pilzinfektionen liefern.

Die tägliche Arbeit von uns Wissenschaftlerinnen und Wissenschaftlern ist, Daten von Experimenten auszuwerten und daraus Theorien oder neue Forschungskonzepte zu entwickeln. Über Verbundvorhaben versuchen wir weitere Kolleginnen und Kollegen aus unterschiedlichen Disziplinen mit ins Boot zu holen, um grundlegend neue Erkenntnisse zu generieren. Die Arbeit von gleich zwei Verbundvorhaben – an denen das Leibniz-HKI maßgeblich beteiligt ist – wurde in den Jahren 2018/19 gewürdigt. Sowohl der Sonderforschungsbereich „ChemBioSys“ mit Christian Hertweck und Georg Pohnert als Sprecher als auch der Leibniz-WissenschaftsCampus InfectoOptics (Sprecher Marc Thilo Figge) erhielten die Finanzierung für die zweite Förderperiode. Meinen herzlichen Glückwunsch an die Verantwortlichen beider Vorhaben.

Darüber hinaus startete Gianni Panagiotou das *BestTreat Innovative Training Network*, das von der Europäischen Kommission mit dem *Horizon 2020* Programm gefördert wird. Unter seiner Leitung schlossen sich Wissenschaftlerinnen und Wissenschaftler an acht europäischen Forschungseinrichtungen und Unternehmen zusammen, um den Einfluss des Darmmikrobioms auf die nicht-alkoholische Fettlebererkrankung zu untersuchen die Diagnose und Therapie der zu verbessern.

„Bestehende Kooperationen vertiefen“

Aufregend ist für uns ebenso die Mitbegründung des neuen Leibniz-Forschungszentrums für Photonik in der Infektionsforschung. Es vertieft die bestehenden Kooperationen zwischen dem Leibniz-IPHT, dem Leibniz-HKI, dem Universitätsklinikum und der Universität Jena und stärkt den Wissenschaftsstandort auf dem Gebiet der Infektionsforschung und insbesondere die Entwicklung neuer diagnostischer Verfahren und Therapien.

Voller Vorfreude blicke ich außerdem auf die Baustelle unseres neuen Leibniz-HKI Biotech Centers. Nach der Grundsteinlegung im Jahr 2019 werden wir es bereits 2021 eröffnen und somit insgesamt 450 Mitarbeiterinnen und Mitarbeitern eine leistungsfähige Infrastruktur zur Verfügung stellen können. Für diese organisatorische Meisterleistung möchte ich mich ganz herzlich bei unserer Verwaltung und insbesondere bei Elke Jäcksch – unserer Verwaltungsdirektorin – bedanken.

„Netzwerke und Strukturen zur Bewältigung der Pandemie“

Und zuletzt muss ich bei meinem Resümee leider auch auf die COVID-19-Pandemie eingehen. Sie war für uns alle präsent und hat uns verdeutlicht, wie bedeutungsvoll Infektionserkrankungen in unserer Zeit immer noch sind. Mit dem von uns geleiteten deutschlandweiten Konsortium InfectControl haben wir schon vor der Pandemie Netzwerke und Strukturen geschaffen, die uns in dieser Lage schnelles Handeln ermöglichten: So haben wir uns in kürzester Zeit mit Partnerinstituten zusammengeschlossen, um verschiedene Projekte und Studien aus den Bereichen Prävention, Diagnostik und Therapie zur Bewältigung der COVID-19-Pandemie zu erarbeiten.

Axel Brakhage, Direktor Leibniz-HKI

PREFACE

Dear Readers,

„New ways for the prevention and therapy of diseases and in environmental protection“

I look back on the past years with very positive feelings: I can literally feel the exhilaration when reminding myself about the summer months of 2018, when we defended the Cluster of Excellence „Balance of the Microverse“. At the same time, I am very grateful that all the efforts were worth it: Because in September, we received the gratifying news that Jena was successful in the Excellence Strategy of the German federal and state governments. „This is the final breakthrough for Jena as an internationally important science location,“ said Thuringia's Minister of Science Wolfgang Tiefensee at the time, and I can only agree. The Leibniz-HKI has played a major role in the success of the Cluster of Excellence. Almost all of our group leaders are involved in the new network and contribute their research ideas to elucidating the function of microbial communities, the microbiomes. I am convinced that this research will open up entirely new avenues for the prevention and therapy of diseases and in environmental protection.

„New impulses in natural products research“

Two female scientists from the Leibniz-HKI set an example at the European level:

Christine Beemelmanns impressed the European Research Council with her MORPHEUS project. With an ERC Starting Grant, she will investigate how marine bacteria control the development of hydroid polyps and protect them with the help of natural antibiotics. Miriam Rosenbaum prevailed in the international competition in a still young field of research: microbial bioelectrochemistry. She was awarded an ERC Consolidator Grant for the e-MICROBe project. Both approaches provide new impulses in natural product research in the search for urgently needed active compounds for medicine. I congratulate Christine Beemelmanns and Miriam Rosenbaum on their well-deserved success.

A highlight was, of course, the visit of ERC President Prof. Jean-Pierre Bourguignon to Leibniz-HKI in November 2018. It was an honor to present the laboratories of the ERC grantees to him and to discuss with him and other Jena ERC grantees about Europe-wide funding and networking of cutting-edge research.

„Approaches for new therapies against life-threatening fungal infections“

When I think of well-deserved success, two other scientists immediately come to my mind: Mark Gresnigt and Matthew G. Blango, for example, who each established a new junior research group at the Leibniz-HKI in 2020. It is in the philosophy of our institute to educate young scientists and at the same time give them the chance to advance their own careers with independent projects.

With the renowned Emmy Noether program, the German Research Foundation supports Mark Gresnigt in establishing his group. Together with his team, he will investigate how the human immune system and pathogenic fungi sense each other. Matthew Blango received funding in the Young Investigator Groups Infection Research program of the German Federal Ministry of Education and Research. He and his team are focusing on the role of RNA in invasive fungal infections. Both junior research groups will bring important insights that will provide new approaches for

therapies against life-threatening fungal infections.

The daily work of us scientists is to evaluate data from experiments and use them to develop hypotheses or new research concepts. Through collaborative projects, we try to bring other colleagues from different disciplines on board to generate fundamentally new insights. The work of two collaborative research projects - in which Leibniz-HKI is significantly involved - was recognized in 2018/19. Both the Collaborative Research Center „ChemBioSys“ headed by Christian Hertweck und Georg Pohnert and the Leibniz ScienceCampus InfectoOptics (Marc Thilo Figge) received funding for the second funding period. My sincere congratulations to those responsible for both projects.

In addition, Gianni Panagiotou acquired funding from the Horizon 2020 program of the European Commission for the BestTreat Innovative Training Network. Under his leadership, scientists at eight European research institutions and companies joined forces to investigate the influence of the gut microbiome on non-alcoholic fatty liver disease and to derive new possibilities for the diagnosis and treatment of the disease.

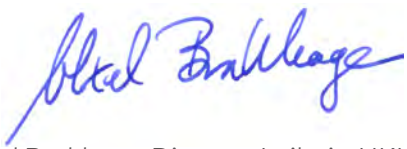
„Strengthening existing cooperations“

Particularly exciting for us is also the co-founding of the new Leibniz Center for Photonics in Infection Research. It deepens the existing collaborations between the coordinating Leibniz-IPHT, the Leibniz-HKI, the University Hospital and the Friedrich Schiller University Jena and strengthens the science location in the field of infection research.

Looking at the construction site of our new Leibniz-HKI Biotech Center also fills me with pride. After laying the foundation stone in 2019, we expect to operate it at the turn of the year 2021/22 and provide our 450 employees with another high-performance infrastructure. I would like to express my sincere thanks to our Administrative Director Elke Jäcksch and her staff for this organizational masterpiece.

„Networks and structures to cope with the pandemic“

The COVID-19 pandemic had a serious impact on the research activities at our institute. In addition to the restrictions that probably every citizen had to experience in their professional and private lives, however, the pandemic impressively showed us how important it is to research infectious diseases and find suitable means to fight them. With the Germany-wide consortium InfectControl, which we lead, we created networks and structures even before the pandemic that enabled us to act quickly in this situation. Thanks to generous and rapid funding decisions, we were able to join forces with partner institutes in a very short time to develop various projects and studies in the areas of prevention, diagnostics and therapy to deal with the COVID-19 pandemic. In this way, our expertise is helping to overcome the global crisis and prevent similar situations in the future.



Axel Brakhage, Director Leibniz-HKI

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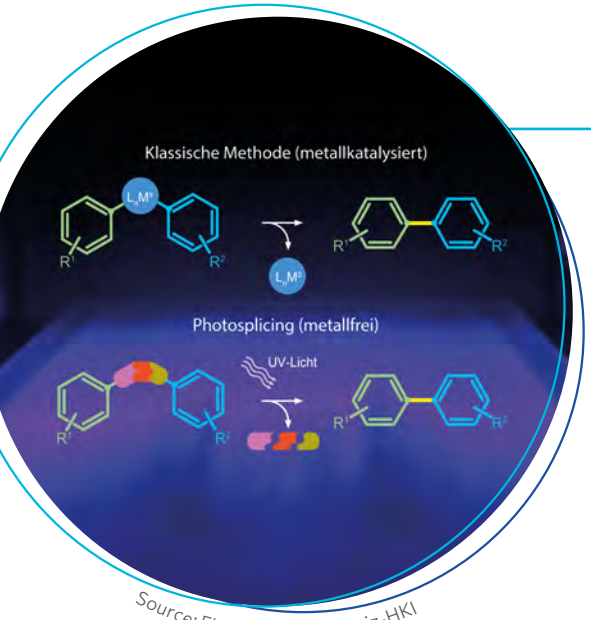
Scientific highlights



Source: Florian Kloß / Leibniz-HKI

Angewandte Chemie International Edition

We developed a method that could revolutionize numerous processes in the chemical industry – the so-called photosplicing. This synthesis method from organic chemistry enables the production of numerous drugs without using toxic heavy metals.

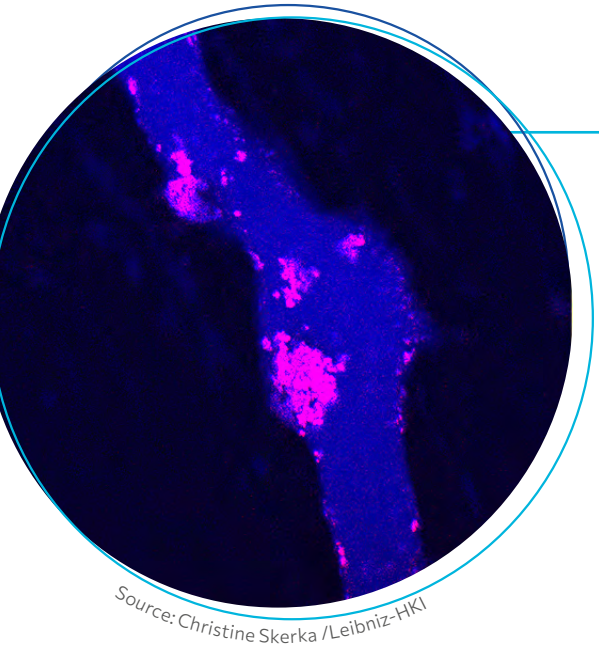
Kloss F, Neuwirth T, Haensch V, Hertweck (2018) Metal-free synthesis of pharmaceutically important biaryls by photosplicing. *Angew Chem Int Ed* 57, 14476-14481.

Source: Ron Hermenau / Leibniz-HKI

Nature Chemical Biology

We have discovered a new iron carrier: the molecule known as gramibactin is formed by bacteria that live in the root zone of corn and wheat. It binds poorly soluble iron from the environment and brings it into the bacterial metabolism. Gramibactin binds iron in a way previously unknown in nature.

Hermenau R, Ishida K, Gama S, Hoffmann B, Pfeifer-Leeg M, Plass W, Mohr JF, Wichard T, Saluz HP, Hertweck C (2018) Gramibactin is a bacterial siderophore with a diazeniumdiolate ligand system. *Nat Chem Biol* 14, 841-843.



Source: Christine Skerka /Leibniz-HKI

Nature Medicine

In collaboration with colleagues from Munich, scientists from the Leibniz-HKI have discovered that the body's own apolipoprotein E acts as a complement inhibitor against the formation of deposits in blood vessels. It also inhibits associated inflammatory reactions.

Yin C, Ackermann S, Ma Z, Mohanta SK, Zhang C, Li Y, Nietzsche S, Westermann M, Peng L, Hu D, Bontha SV, Srikakulapu P, Beer M, Megens RTA, Steffens S, Hildner M, Halder LD, Eckstein HH, Pelisek J, Herms J, Roeber S, Arzberger T, Borodovsky A, Habenicht L, Binder CJ, Weber C, Zipfel PF, Skerka C, Habenicht AJR (2019) ApoE attenuates unresolvable inflammation by complex formation with activated C1q. *Nat Med 25, 496-506.*

Source: Jan-Peter Kasper / FSU Jena

Cell Chemical Biology

An international research team with the participation of Axel Brakhage and Christian Hertweck has found out how the pathogenic mold *Aspergillus fumigatus* triggers the immune defense. In the process, the group clarified the mode of action of the mold toxin gliotoxin.

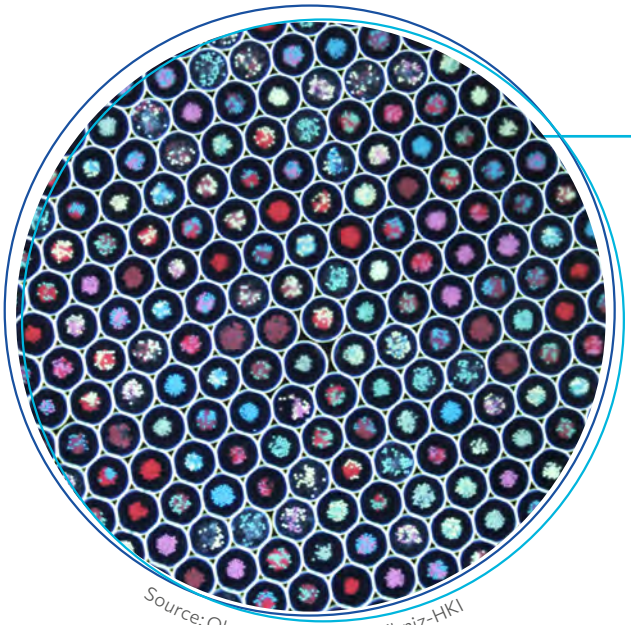
König S, Pace S, Pein H, Heinekamp T, Kramer J, Romp E, Straßburger M, Troisi F, Proschak A, Dworschak J, Scherlach K, Rossi A, Sautebin L, Haeggström JZ, Hertweck C, Brakhage AA, Gerstmeier J, Proschak E, Werz O (2019) Gliotoxin from Aspergillus fumigatus abrogates leukotriene B4 formation through inhibition of leukotriene A4 hydrolase. *Cell Chem Biol* 26, 524-534.

Source: Leibniz-HKI

Cell

A team of researchers from Leibniz-HKI, the University of Jena, and other institutions across Germany deciphered a mechanism by which certain microbiomes amplify inflammatory responses in the lung.

Bacher P, Hohnstein T, Beerbaum E, Röcker M, Kaufmann S, Brandt C, Röhmel J, Stervbo U, Nienen M, Babel N, Milleck J, Assenmacher M, Cornely OA, Heine G, Worm M, Creutz P, Tabeling C, Ruwwe-Glösenkamp C, Sander LE, Brunke S, Hube B, Blango M, Kniemeyer O, Brakhage AA, Schwarz C, Scheffold A (2019) Instruction of human anti-fungal Th17 immunity and immune pathology by cross-reactivity against a single member of the microbiota. *Cell* 176, 1340-1355.



Source: Oksana Shvydkiv / Leibniz-HKI

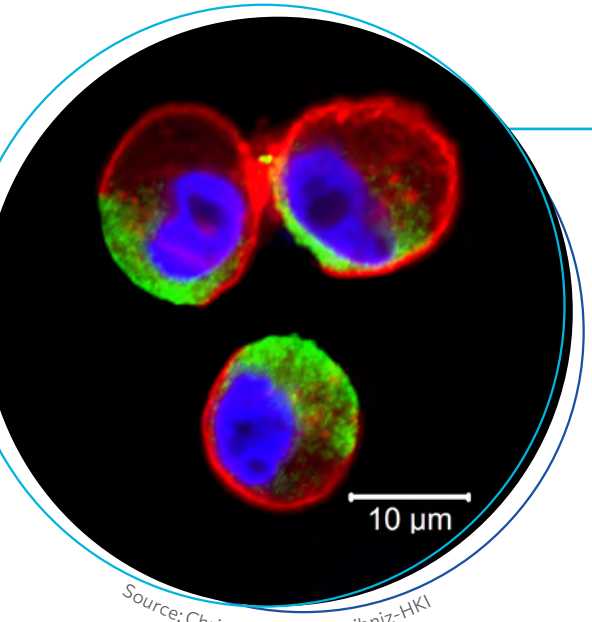
Small

Together with scientists from the University of Jena we have developed a method to distinguish individual droplets in microfluidics using artificial intelligence.

Svensson CM, Shvydkiv O, Dietrich S, Mahler L, Weber T, Choudhary M, Tovar M, Figge MT, Roth M (2019) Coding of experimental conditions in microfluidic droplet assays using colored beads and machine learning supported image analysis. *Small* 15(4), e1802384.

HIGHLIGHTS

Scientific highlights

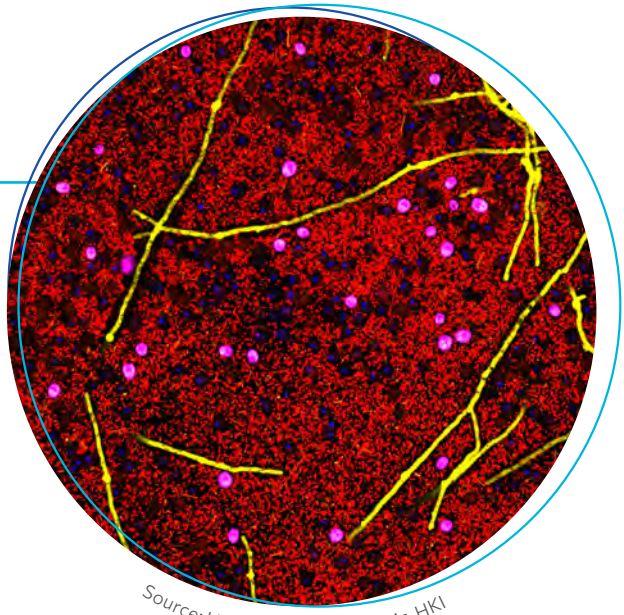


Source: Christine Skerka/Leibniz-HKI

Nature Communications

We identified a human protein that triggers autoinflammatory reactions. This is particularly problematic in chronic diseases: If inflammation is otherwise part of the healing process, it worsens the situation in patients with chronic vascular inflammation, for example.

Irmscher S, Brix SR, Zipfel SLH, Halder LD, Mutlutürk S, Wulf S, Girdauskas E, Reichenspurner H, Stahl RAK, Jungnickel B, Wiech T, Zipfel PF, Skerka C (2019) Serum FHR1 binding to necrotic-type cells activates monocytic inflammasome and marks necrotic sites in vasculopathies. *Nat Commun* 10, 2961.



Source: Hanno Schoeler/Leibniz-HKI

Cell Metabolism

A team of scientists found evidence that the composition of the gut microbiome plays a crucial role in whether exercise can protect against type II diabetes.

Liu Y, Wang Y, Ni Y, Cheung CKY, Lam KSL, Wang Y, Xia Z, Ye D, Guo J, Tse MA, Panagiotou G, Xu A (2019) Gut microbiome fermentation determines the efficacy of exercise for diabetes prevention. *Cell Metab* 3, 77-91.e5.

Source: Felix Blei/FSU Jena

Angewandte Chemie International Edition

Together with researchers from the University of Jena we studied the blue discoloration of a fungus of the genus *Psilocybe* after injury, providing an explanation for the formation of psilocybin - the highly hallucinogenic substance that gives „magic mushrooms“ their effect.

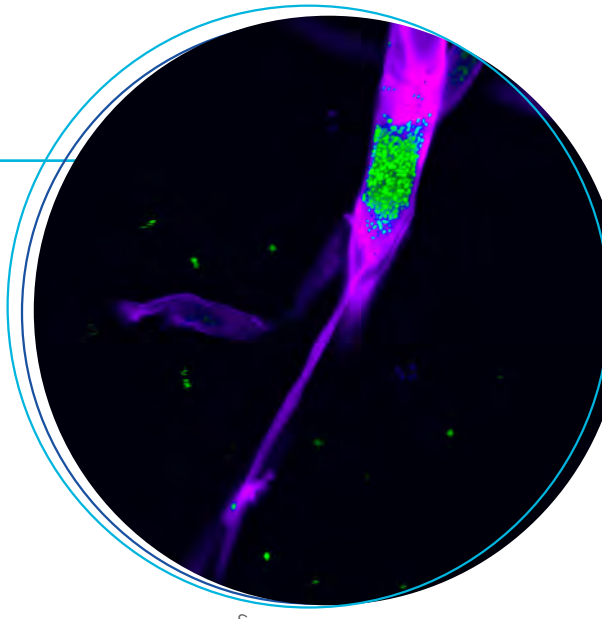
Lenz C, Wick J, Braga D, Garcia-Altares M, Lackner G, Hertweck C, Gressler M, Hoffmeister D (2019) Injury-triggered blueing reactions of *Psilocybe* „magic“ mushrooms. *Angew Chem Int Ed* 59, 1450-1454.

Source: Chemical Science Journal / Stallforth et al. (2019)

Chemical Science Journal

Biochemists from Jena investigated how the biosynthesis of natural products changed in the course of evolution in order to detect active compounds. Among other things, the new substances could be used as urgently needed new antibiotics or cancer drugs.

Götze S, Arp J, Lackner G, Zhang S, Kries H, Klapper M, García-Altares M, Willing K, Günther M, Stallforth P (2019) Structure elucidation of the Syringafactin lipopeptides provides insight in the evolution of nonribosomal peptide synthetases. *Chem Sci* 10, 10979-10990.

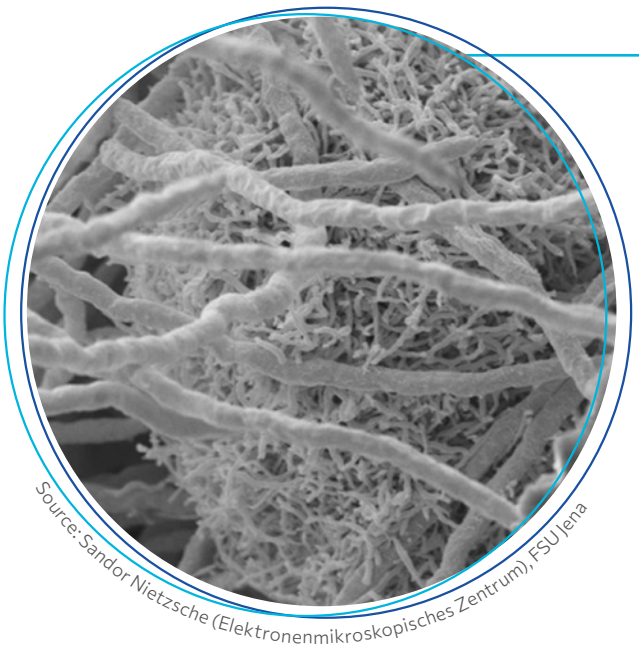


Source: Leibniz-HKI

Angewandte Chemie International Edition

The bite of a spider caused a severe inflammation in an Australian woman. The tragic course of the infection led an international team of researchers with the participation of Leibniz-HKI to new active substances - the so-called necroximes. The substances are produced by bacteria that live inside fungi. Scientists isolated them from the patient's infected forearm tissue. The highly effective cytotoxins may provide clues for the development of new cancer drugs.

Niehs SP, Dose B, Richter R, Pidot SJ, Dahse H-M, Stinear TP, Hertweck C (2020) Mining symbionts of spider-transmitted fungus illuminates uncharted biosynthetic pathways to cytotoxic benzolactones. *Angew Chem Int Ed* 59, 7766-7771.



Source: Sandor Nietzsche (Elektronenmikroskopisches Zentrum), FSU Jena

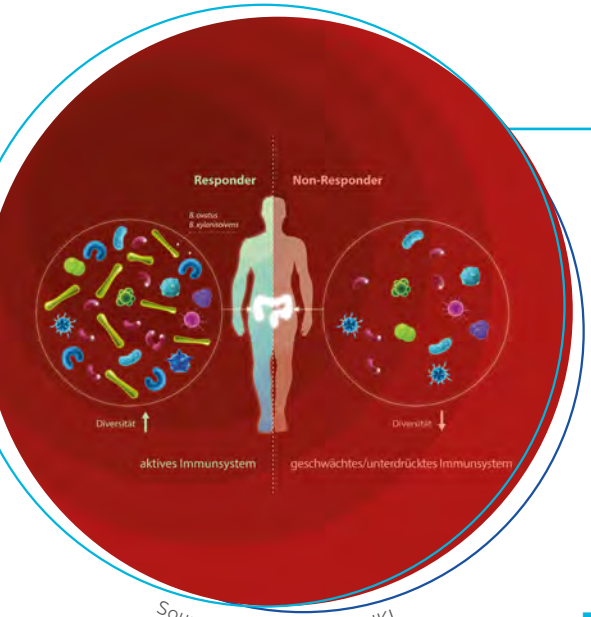
eLife

If the bacterium *Streptomyces rapamycinicus* and the fungus *Aspergillus fumigatus* are in direct contact, the bacterium stimulates the fungus to produce fumigermin. We discovered this new natural product, which prevents the germination of the bacterium's spores. In this way, the fungus gets rid of its unwelcome food competitor.

Stroe MC, Netzker T, Scherlach K, Krüger T, Hertweck C, Valiante V, Brakhage AA (2020) Targeted induction of a silent fungal gene cluster encoding the bacteria-specific germination inhibitor fumigermin. *eLife* 9, e52541.

HIGHLIGHTS

Scientific highlights



Source: Luo Yu / Leibniz-HKI

Microbiome

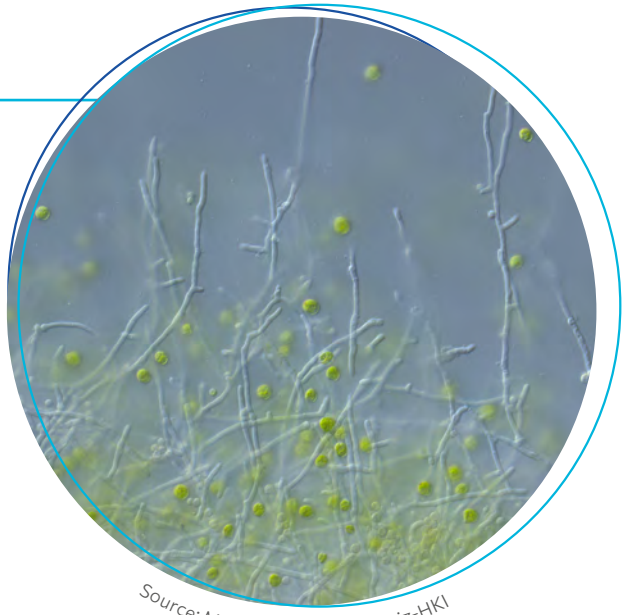
Cancer patients have varying success rates in responding to therapies. How successful the classic treatment methods are may be based on the composition of the microbiome in the gut. This is indicated by results from scientists at Leibniz-HKI and from Hong Kong.

Heshiki Y, Vazquez-Uribe R, Li J, Ni Y, Quainoo S, Imamovic L, Li J, Sørensen M, Chow BKC, Weiss GJ, Xu A, Sommer MOA, Panagiotou G (2020) Predictable modulation of cancer treatment outcomes by the gut microbiota. *Microbiome* 8, 28.

The ISME Journal

A research team from the Leibniz-HKI and the University of Jena investigated the complex interaction between a bacterium, a fungus and a plant: bacteria of the genus *Streptomyces* form numerous active compounds that ensure their survival in nature. For example, the azalomycins produced by some streptomyces are antimicrobially active and also damage cells of higher organisms, including the green alga *Chlamydomonas reinhardtii.* The alga actively forms a partnership with the mold *Aspergillus nidulans* and is thus protected from the damaging effect of azalomycin F.

Krespach MKC, García-Altares M, Flak M, Schoeler H, Scherlach K, Netzker T, Schmalzl A, Mattern DJ, Schroeckh V, Komor A, Mittag M, Hertweck C, Brakhage AA (2020) Lichen-like association of *Chlamydomonas reinhardtii* and *Aspergillus nidulans* protects algal cells from bacteria. *ISME J* 14, 2794-2805.



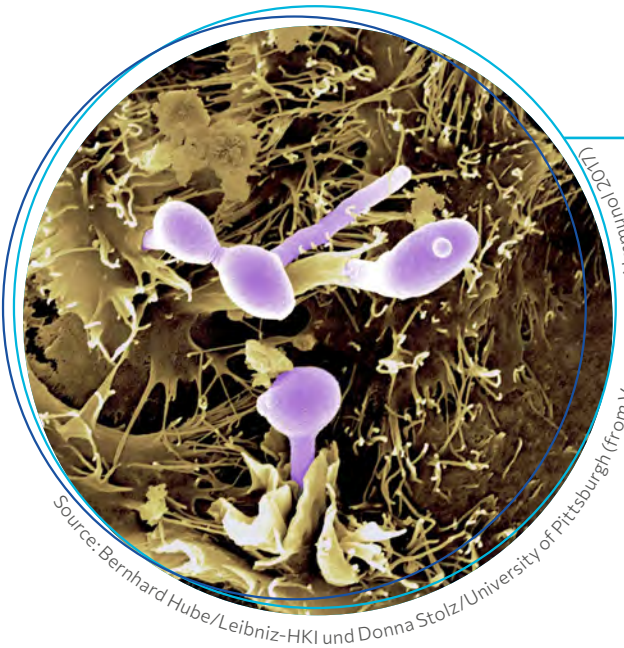
Source: Mario Krespach / Leibniz-HKI

Source: Leibniz-HKI

PNAS

We took a closer look at the molecular mechanism of a microbial triangular relationship. The bacterium *Pseudomonas tolaasii* triggers brown spot disease in cultivated mushrooms and thus causes considerable harvest losses. But the fungus has supporters: bacteria of the genus *Mycetocola* inactivate a toxin of the bacterium and another active ingredient that serves to inhibit the mobility and spread of the bacterial pathogen. This protective principle could be a model for applications in agriculture or medicine.

Hermenau R, Kugel S, Komor AJ, Hertweck C (2020) Helper bacteria halt and disarm mushroom pathogens by linearizing structurally diverse cyclopeptides. *Proc Natl Acad Sci* 117, 23802-23806.



Source: Bernhard Hube/Leibniz-HKI und Donna Stolz/University of Pittsburgh (from Verma et al., Sci Immunol 2017)

Microbiome

In a combination of bioinformatic analyses and laboratory experiments, an international team of researchers with participation of the Leibniz-HKI showed that the peaceful coexistence of bacteria and fungi in the digestive system changes into a competitive situation due to antibiotic treatment. This could subsequently favor fungal infections.

Seelbinder B, Chen J, Brunke S, Uribe RV, Meyer AC, de Oliveira Lino FS, Chan KF, Loos D, Imamovic L, Tsang CC, Lam RPK, Sridhar S, Kang K, Hube B, Woo PCY, Sommer MOA, Panagiotou G (2020) Antibiotics create a shift from mutualism to competition in human gut communities with a longer-lasting impact on fungi than bacteria. *Microbiome* 8, 133.

Cell Reports

Infections with two pathogens are a major problem in the clinic. Researchers from Würzburg and Jena have developed a technique that provides new insights into these processes. It is also suitable as an early warning system.

Seelbinder B*, Wallstabe J*, Marischen L*, Weiss E, Wurster S, Page L, Löffler C, Bussemer L, Schmitt AL, Wolf T, Linde J, Cicin-Sain L, Becker J, Kalinke U, Vogel J, Panagiotou G, Einsele H, Westermann AJ*, Schäuble S*, Loeffler L* (2020) Triple RNA-seq reveals synergy in a human virus-fungus co-infection model. *Cell Rep* 33, 108389. (*equal contribution)

Source: Leibniz-HKI

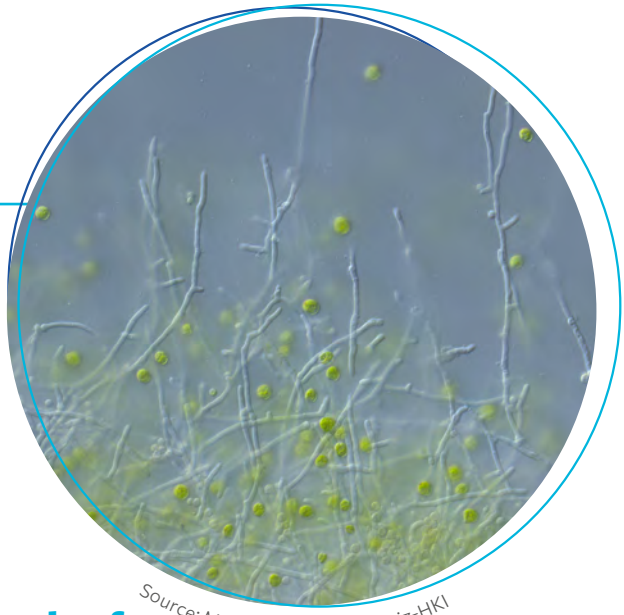
HIGHLIGHTS

Awards

Source: Anna Schroll / Leibniz-HKI

DECHEMA Naturstoffpreis 2019

Pierre Stallforth received the DECHEMA Young Scientist Award for Natural Product Research 2019. Stallforth has elucidated the function of bacterial secondary metabolites in complex ecological scenarios. In addition to the biological and ecological roles of diverse bacterial natural products, Pierre Stallforth also successfully investigated the biological functions of signaling molecules in amoebae.



Source: Mario Krespach / Leibniz-HKI

Leibniz Drug of the Year 2019

The newly discovered compound Gramibactin received the award „Leibniz Drug of the Year 2019“.

Source: Gerhard Müller

Two Science Awards of the Beutenberg Campus

Susanne Ackermann convinced the jury with her doctoral thesis „The role of apolipoprotein E in the human immune response“. She identified apolipoprotein E - ApoE for short - as an inhibitor of the human complement system that can prevent the formation of deposits in blood vessels.

By researching combinations of active compounds, Pierre Stallforth deviates from common practice, in which single substances are usually investigated. In a paper published in the scientific journal *PNAS*, he showed that combinations of several active compounds can produce cooperative and synergistic effects and thus potentially facilitate the treatment of resistant pathogens. His work also convinced the jury.

Source: Leibniz-HKI

Medac Research Award

Questions in the natural sciences are very complex. Therefore, their investigation and answering is usually only possible in collaboration of many scientists. In order to promote these collaborations, medac GmbH offers annual prize money of 10,000 euros for the most successful team-based research projects.

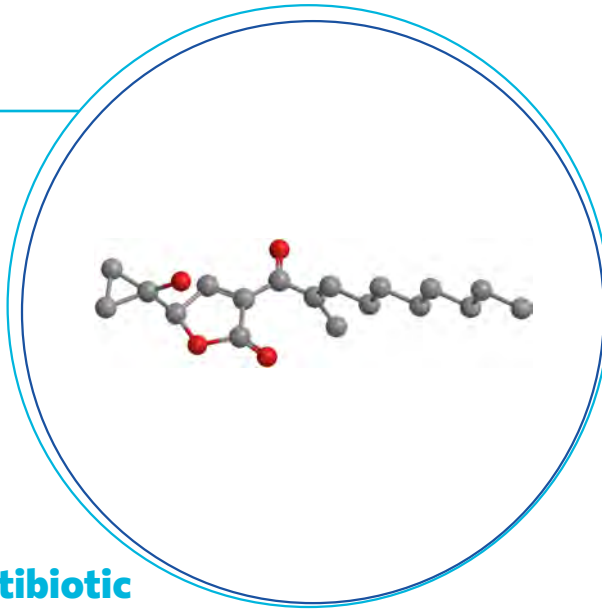
Trottmann F, Franke J, Richter I, Ishida K, Cyrulies M, Dahse HM, Regestein L, Hertweck C (2019) Cyclopropanol Warhead in malleicyprol confers virulence of human- and animal-pathogenic *Burkholderia* species. *Angew Chem Int Ed Engl* 58(40), 14129-14133.

Svensson CM*, Shydkiv O*, Dietrich S, Mahler L, Weber T, Choudhary M, Tovar Mº, Figge MT**º, Roth M** (2019) Coding of experimental conditions in microfluidic droplet assays using colored beads and machine learning supported image analysis. *Small* 15, e1802384. ; *equal contribution; ºcorresponding authors; **equal contribution

Braga D, Last D, Hasan M, Guo H, Leichnitz D, Uzum Z, Richter I, Schalk F, Beemelmanns C, Hertweck C, Lackner G (2019) Metabolic pathway rerouting in *Paraburkholderia rhizoxinica* evolved long-overlooked derivatives of coenzyme F_{420}. *ACS Chem Biol* 14(9), 2088-2094.

Leibniz Drug of the Year 2020

We identified substances formed by the bacteria of the genus *Burkholderia*, so-called malleicyproles. Initial studies show that they contribute to their pathogenic effect. The group led by Christian Hertweck thus closes the knowledge gap on the so-called virulence factors of the bacteria. The malleicyproles have been selected as Leibniz Drug of the Year 2020.



Source: Leibniz-HKI

Source: Guido Werner/GWP

Tuberculosis antibiotic BTZ-043

The new active compound against tuberculosis pathogens is the **innovation of the year 2019** in Central Germany. The substance discovered at the Leibniz-HKI, called BTZ-043, has a completely new mechanism of action and is therefore also effective against resistant strains of tuberculosis.

Crucial step in the development of a promising compound: **BTZ-043 was administered to patients** for the first time in Cape Town in 2019.

HIGHLIGHTS

Scientific conferences

Source: Steffen Walther

Infectious Diseases in the 21st Century

Infectious diseases are once again a serious threat - fueled by improper use of medicines, vaccination gaps and increased mobility. In October 2018, international experts discussed the latest research findings from infection research and measures to combat infections. A special highlight was the public evening lecture by Nobel laureate Harald zur Hausen.

Source: Leibniz-HKI

International VAAM Workshop 2019 - Biology of Microorganisms Producing Natural Products

In September 2019, experts in microbiology, chemistry or bioinformatics met at Leibniz-HKI to discuss the biosynthesis and synthetic biology of bioactive natural compounds.

Source: FSU Jena

Microverse I – Joint International Symposium on Microbial and Biomolecular Interactions

The conference brought together national and international scientists to discuss recent advances in microbial communication, host-microbiome interactions and environmental microbiomes. Due to the Corona pandemic, the symposium was held digitally.

Public events

Source: Leibniz-HKI

Lange Nacht der Wissenschaften

Before the Corona pandemic restricted us in many areas, we always took the opportunity to engage in direct dialogue with the public and talk about our research.

In fall 2019, for example, we welcomed around 500 visitors to the **Long Night of Science in Jena**. People were thus able to get their own impression of natural product research as well as research on human pathogenic fungi in our laboratories.

Forsche Schüler Tag

The Leibniz-HKI opened its (laboratory) doors again in 2018 and 2019 for interested and curious people for the "**Forsche Schüler Tag**". Studentsfrom various Jena schools were allowed to experiment, ask questions about professions and get to know the work at the Leibniz-HKI.

Source: Hanna Heidel-Fischer/Leibniz-HKI

Source: Heiner Witte

MS Wissenschaft

Since July 2020, the **MS Wissenschaft** has been touring through Germany and the Leibniz-HKI is on board. In line with this year's theme of bioeconomy of the hands-on exhibition, polyhydroxybutyric acid is presented as an alternative to conventional plastics and the earth battery as a way to generate electricity from bacteria.

HIGHLIGHTS

Source: Anna Schroll / Leibniz-HKI

Recognition for Axel Brakhage

Twelve years after his admission to the National Academy of Sciences Leopoldina, Axel Brakhage was elected to the **Senate of the Academy**. As chairman and senator of Section 13 - Microbiology and Immunology, he represents the interests of the members of this section before the presidium. His term of office begins on March 4 and lasts four years.

The **DFG**'s General Assembly elected Axel Brakhage to the **Executive Committee** of the largest research funding organization and central self-governing body for science in Germany.

Equal opportunities

We and the two other Leibniz Institutes in Jena have been awarded the "Total E-Quality" predicate (TEQ) for our forward-looking and sustainably effective personnel policy. This is the third time that the national association "Total E-Quality Deutschland" has certified our research institutes' successful efforts to treat men and women equally, to promote diversity, and to create the conditions for employees to achieve a good work-life balance.

Source: Kai Neunert/TOTAL E-QUALITY Deutschland e. V.

Department

BIOMOLECULAR CHEMISTRY

BIOMOLECULAR CHEMISTRY

Mission

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.

Most important results

Research in the Department of Biomolecular Chemistry (BMC) 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. A specialty of the group are their pioneering studies on "exotic" microorganisms beyond the typical producer strains as sources of therapeutics, e.g. *Burkholderia*, *Erwinia* and *Janthinobacterium* spp., as well as anaerobes (*Clostridium* spp.). Since genome analyses have revealed that their full biosynthetic potential is much larger than expected, the BMC group employs diverse strategies to unearth cryptic natural products, such as genome mining, pathway engineering and triggering, as well as co-cultivation approaches. In particular, we 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. These highly interdisciplinary studies often result from collaboration with excellent international and national work groups. A high number of joint publications result from close collaborations within the Leibniz-HKI and the Friedrich Schiller University Jena (FSU). International visibility of the work is documented by frequent citations (around 2000 per year, Google Scholar), and outstanding Altmetric Scores, placing over a dozen of the papers presented below among the top 5% of all research output worldwide. The BMC group is involved in numerous important networks, such as InfectControl (DrugBioTune), Cluster of Excellence "Balance of the Microverse" (founding member), SFB 1127 ChemBiosys (speaker), PAKT für Forschung und Innovation (initiator), and the Jena School for Microbial Communication (JSMC). Research in 2018–20 has also been funded by the Leibniz Prize (to CH), as well as Alexander von Humboldt and Marie Skłodowska-Curie fellowships (EU).

Ecology- and genomics-driven natural product discovery: Genome mining and chemical analyses revealed that rhizosphere bacteria (*Paraburkholderia graminis*) produce a new type of siderophore, gramibactin, a lipodepsipeptide that efficiently binds iron with unusual *N*-nitrosohydroxylamine (diazeniumdiolate) moieties. In collaboration with the former

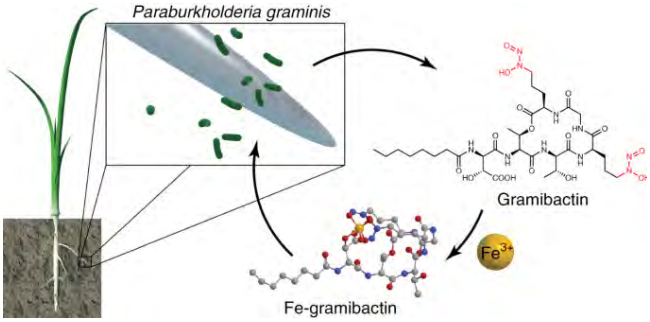


Figure: Gramibactin is a bacterial siderophore with a diazeniumdiolate ligand system (Hermenau *et al.*, *Nat Chem Biol* 2018).

department Cell and Molecular Biology (Hans-Peter Saluz, Leibniz-HKI), iron uptake into the plant was monitored by PET-CT. We found that gramibactin biosynthesis genes are conserved in numerous plant-associated bacteria associated with rice, wheat, and maize, which may utilize iron from the complex.

Notably, iron availability is essential for photosynthesis, plant growth and thus has a major impact on crop yields (*Nat Chem Biol* 2018). By mutational analysis, we identified genes necessary for diazeniumdiolate formation. Genome mining revealed a broad range of orthologous gene clusters in mainly plant-associated *Burkholderia/Paraburkholderia* species. Several new diazeniumdiolate siderophores were fully characterized. *In vitro* assays and *in vivo* monitoring experiments showed that these unusual iron chelators liberate nitric oxide (NO) in plant roots. This finding is important since NO donors are considered as biofertilizers that maintain iron homeostasis and increase overall plant fitness (*Angew Chem Int Ed* 2019c).

In collaboration with the Kaltenpoth laboratory (University of Mainz, now Jena), we reported a successful case of ecology-driven discovery of novel antimicrobial agents. Symbiotic bacteria (*Burkholderia gladioli*) protect the vulnerable egg stage of herbivorous beetles against detrimental microbes, in particular pathogenic fungi. In addition to a blend of antibiotics we isolated a novel antifungal polyketide (lagriamide) from egg clutches inhabited by an uncultured, protective symbiont, which is dominant in field-collected *Lagria villosa* (*Nat Commun* 2018a), and thus mediates this defensive role. Genome mining of one of the protective symbionts (*Burkholderia gladioli*) of the invasive beetle revealed a cryptic gene cluster that codes for the biosynthesis of a novel antifungal polyketide with a glutarimide pharmacophore. Targeted gene inactivation, metabolic profiling, and bioassays led to the discovery of the gladiofungins as previously-overlooked components of the antimicrobial armory of the beetle symbiont, which are highly active against the entomopathogenic fungus *Purpureocillium lilacinum*. By mutational analyses, isotope labeling, and computational analyses of the modular polyketide synthase, we found that the rare butenolide moiety of gladiofungins derives from an unprecedented polyketide chain termination reaction involving a glycerol-derived C3 building block. The key role of an A-factor synthase (AfsA)-like offloading domain was corroborated by CRISPR-Cas-mediated gene editing, which facilitated precise excision within a PKS domain (*Angew Chem Int Ed* 2020a).

In collaboration with the Wilkinson and Hutchins laboratories (John Innes Centre and University of East Anglia) it was shown that a parasitic fungus (*Escovopsis*) upregulates the production of two specialized metabolites when it infects the cultivar of leafcutter ants (*Acromyrmex*). These compounds inhibit a protective *Pseudonocardia* symbiont and reduce ant worker behavioral defenses and is ultimately lethal when it accumulates in ant tissues. These results are consistent with an active evolutionary arms race between *Pseudonocardia* and *Escovopsis*, which modifies both bacterial and behavioral defenses such that colony collapse is unavoidable once *Escovopsis* infections escalate (*Nat Commun* 2018b).

Mining the genome of the food-spoiling bacterium *Burkholderia gladioli* pv. *cocovenenans* revealed five nonribosomal peptide synthetase (NRPS) gene clusters, including an orphan gene locus (*bol*). Gene inactivation and metabolic profiling linked the *bol* gene cluster to novel bolaamphiphilic lipopeptides with antimycobacterial activity. A combination of chemical analysis and bioinformatics elucidated the structures of bolagladin A and B, lipocyclopeptides featuring an unusual dehydro-beta-alanine enamide linker fused to an unprecedented tricarboxylic fatty acid tail. Through a series of targeted gene deletions, we proved the involvement of a designated citrate synthase (CS), priming ketosynthases III (KS III), a type II NRPS, including a novel desaturase for enamide formation, and a multimodular NRPS in generating the cyclopeptide. Network analyses revealed the evo-

lutionary origin of the CS and identified cryptic CS/NRPS gene loci in various bacterial genomes (*Angew Chem Int Ed* 2020b).

A spider-transmitted fungus (*Rhizopus microsporus*) that was isolated from necrotic human tissue was found to harbor endofungal bacteria (*Burkholderia* sp.). Metabolic profiling of the symbionts revealed a complex of cytotoxic agents (necroximes). Their structures were characterized as oxime-substituted benzolactone enamides with a peptidic side chain. The potently cytotoxic necroximes are also formed in symbiosis with the fungal host and could have contributed to the necrosis. Genome sequencing and computational analyses revealed a novel modular PKS/NRPS assembly line equipped with several non-canonical domains. Based on gene-deletion mutants, we propose a biosynthetic model for bacterial benzolactones. We identified specific traits that serve as genetic handles to find related salicylate macrolide pathways (lobatamide, oximidine, apicularen) in various other bacterial genera. Knowledge of the biosynthetic pathway enables biosynthetic engineering and genome-mining approaches (*Angew Chem Int Ed* 2020c).

Elucidation of virulence factors and antivirulence strategies: *Burkholderia* species such as *B. mallei* and *B. pseudomallei* are bacterial pathogens causing fatal infections in humans and animals (glanders and melioidosis), yet knowledge on their virulence factors is limited. While pathogenic effects have been linked to a highly conserved gene locus (bur/mal) in the *B. mallei* group, the metabolite associated to the encoded polyketide synthase, burkholderic acid (syn. malleilactone), could not explain the observed phenotypes. By metabolic profiling and molecular network analyses of the model organism *B. thailandensis*, the primary products of the cryptic pathway were identified as unusual cyclopropanol-substituted polyketides (malleicyprols). Cell-based assays and a nematode infection model showed that the malleicyprol confers cytotoxicity and virulence (*Angew Chem Int Ed* 2019a). In collaboration with the Pohnert (FSU) and the Kries (Leibniz-HKI) labs we gained first insight into the biosynthetic origin of their cyclopropanol warhead. By a combination of mutational analysis and metabolomics we found that sulfonium acids, dimethylsulfoniumpropionate (DMSP) and gonyol, known as osmolytes and as crucial components in the global organosulfur cycle, are key intermediates en route to the cyclopropanol unit. Functional genetics and *in vitro* analyses uncover a specialized pathway to DMSP and show that DMSP is loaded onto the NRPS-PKS hybrid assembly line by an adenylation domain dedicated to zwitterionic starter units. Then, the megasynthase transforms DMSP into gonyol, as demonstrated by heterologous pathway reconstitution in *E. coli* (*Angew Chem Int Ed* 2020d).

Siderophores are key players in bacteria-host interactions, with the main function to provide soluble iron for their producers. By targeted gene activation and *in vitro* studies our group revealed that the cell-to-cell signaling molecule and disease mediator IQS (aeruginaldehyde) of the human pathogen *Pseudomonas aeruginosa* and related bacteria actually derives from the siderophore pyochelin. Furthermore, addition of IQS to bacterial cultures (*Burkholderia thailandensis*) showed that the signaling molecule is captured by a congener of another siderophore family, malleobactin, to form a nitrone conjugate (malleonitrone) that is active against the IQS-producer. Thus, we uncovered complex communication processes with derailed siderophore functions, a novel nitrone bioconjugation, and a new type of antibiotic against Gram-negative bacteria (*Angew Chem Int Ed* 2019b). Our group has found that the antimetabolite 6-thioguanine (6TG) is critical virulence factor of *Er-*

winia amylovorans, a plant pathogen that causes fire blight. We identified a specialized bipartite enzyme system, consisting of an ATP-dependent sulfur transferase (YcfA) and a sulfur-mobilizing enzyme (YcfC), that is responsible for the peculiar oxygen-by-sulfur substitution found in the biosynthesis of 6TG. Mechanistic and phylogenetic studies revealed that YcfA-mediated 6TG biosynthesis evolved from ancient tRNA modifications that support translational fidelity (*Angew Chem Int Ed* 2018c).

The bacterial pathogen *Pseudomonas tolaasii* severely damages white button mushrooms by secretion of the pore-forming toxin tolaasin, the main virulence factor of brown blotch disease. Yet, fungus-associated helper bacteria of the genus *Mycetocola (M. tolaasinivorans* and *M. lacteus)* may protect their host by an unknown detoxification mechanism. By a combination of metabolic profiling, imaging mass spectrometry, structure elucidation, and bioassays, we found that the helper bacteria inactivate tolaasin by linearizing the lipocyclopeptide. Furthermore, we found that *Mycetocola* spp. impair the dissemination of the pathogen by cleavage of the lactone ring of pseudodesmin. The role of pseudodesmin as a major swarming factor was corroborated by identification and inactivation of the corresponding biosynthetic gene cluster. Activity-guided fractionation of the *Mycetocola* proteome, matrix-assisted laser desorption/ionization (MALDI) analyses, and heterologous

enzyme production identified the lactonase responsible for toxin cleavage. We revealed an antivirulence strategy in the context of a tripartite interaction that has high ecological and agricultural relevance (*Proc Nat Acad Sci USA* 2020a).

Antibiotics from anaerobes: We continued mining the hidden biosynthetic potential of anaerobic bacteria, which represent an underexplored source of bioactive natural products. Our efforts led to the isolation and structure elucidation of a novel antimycobacterial natural product, clostroindolin, produced by *Clostridium beijerinckii*, which might inspire the development of novel antibiotics (*Org Biomol Chem* 2019). In addition, we discovered various antimicrobial acyloin natural products from *C. beijerinckii* strains with activities against mycobacteria and pseudomonas (*ACS Chem Biol* 2019a). We also made significant progress in the elucidation of biosynthetic pathways to antibiotics in anaerobes. On the basis of our recent discovery of the biosynthetic gene cluster for the thioamidated peptide antibiotic closthioamide (CTA) we elucidated the enzyme responsible for thioamide formation. The Gram-positive obligate anaerobe *Ruminiclostridium cellulolyticum* produces this promising drug candidate by means of a non-canonical peptide assembly line that markedly differs from known nonribosomal peptide synthetases. These findings provide the first insights into the biosynthesis of thioamide-containing nonribosomal peptides and offers a starting point for the discovery related natural products (*Angew Chem Int Ed* 2018d). Genome editing, biochemical assays, and mutational studies were used to demonstrate that an Fe-S cluster containing member of the adenine nucleotide α-hydrolase protein superfamily (CtaC) is responsible for sulfur incorporation. The reconstitution of CtaC provides the first example of a NRP thioamide synthetase. Using CtaC as a bioinformatic handle, we demonstrate that thioamidated NRP biosynthetic gene clusters are more widespread than previously appreciated (*Angew Chem Int Ed* 2019d). Furthermore, we gained insight into that assembly of the polythioamide antibiotic backbone formation by an unusual thiotemplated assembly strategy. Through the use of *in vitro* biochemical assays, we demonstrate that the amide backbone of CTA is assembled in an unusual thiotemplated pathway involving the cooperation of a transacylating member of the papain-like cysteine protease family and an iteratively acting ATP-grasp protein. Using this information, we identified hundreds of such thiotemplated yet nonribosomal peptide synthetase (NRPS)-independent biosynthetic gene clusters across diverse bacterial phyla. The data presented herein not only clarify the pathway for the biosynthesis of CTA, but also provide a foundation for the discovery of additional secondary metabolites produced by noncanonical biosynthetic pathways (*Proc Nat Acad Sci USA* 2020b).

Natural product biosynthesis: Research in this area focused on the enzymatic conversions that lead to biologically active compounds, with emphasis on evolutionary aspects. In collaboration with the Tsunematsu/Watanabe groups (University of Shizuoka, Japan) we studied the formation of halogenated mycotoxins produced by an important fungus used in food fermentation (*Aspergillus oryzae*). A remarkable biosynthetic conversion in the aspirochlorine pathway is a “peptide editing” step. The installation of the N-methoxylation of the peptide bond sets the stage for a retro-aldol reaction that leads to a formal Phe-to-Gly conversion. The substrate scopes of the dedicated enzymes as well as bioassays revealed that the peptide editing has evolved to optimize the antifungal action of the natural product (*Angew Chem Int Ed* 2018a). A specialized “on-line” polyketide modification has, on the other hand, emerged from classical

ketosynthases (KS). We gained new insight into the biosynthesis of the pharmacophoric lactone residue of the antimitotic and antifungal agent rhizoxin. The KS of the branching module mediates a Michael addition for chain branching as well as the subsequent lactonization and tolerates defined acyl chain lengths to produce five- to seven-membered lactones. This unusual, TE-independent on-line cyclization is relevant for synthetic biology approaches (*Angew Chem Int Ed* 2018b). Important lessons on the evolution of polyketide diversity were learned from the rational engineering of bacterial modular type I polyketide synthases (PKSs). These complex natural produces play eminent roles in the development of medicines. We succeeded in an evolution-guided morphing of modular PKSs inspired by natural recombination processes. By deletion and insertion of PKS modules we interconverted the assembly lines for related antibiotic and antifungal agents, aureothin (*aur*) and neoaureothin (*nor*), in both directions. Mutational and functional analyses of the polyketide-tailoring cytochrome P450 monooxygenases, and PKS phylogenies gave clues on potential evolutionary scenarios. The KS-AT linker proves to be well suited as fusion site, which supports a model for alternative module boundaries in some PKS systems. These findings may guide future engineering approaches (*Nat Commun* 2019).

Synthetic routes to pharmaceuticals: A C-S bond plays a key role in the serendipitous discovery of a novel metal-free cross-coupling method ("photosplicing") to prepare pharmaceutically relevant biaryls. To date benchmark methods for biaryl synthesis have relied on highly toxic heavy metal catalysts, which are unfavorable in the synthesis of pharmaceuticals. Our new method involves the tethering of two phenyl groups by a temporary, traceless sulfonamide linker that directs a photochemical aryl fusion with perfect regio- and chemoselectivity. Using a flow reactor we synthesized numerous biaryl building blocks for important therapeutics in high yields, such as antibiotics, antitumor, neuroprotective and cholesterol-lowering agents as well as antiarthritic non-steroidal antiinflammatory drugs (NSAIDs). The new method was also successfully employed in a total synthesis of cannabinol, an important analgesic and antiemetic therapeutic, and of key building blocks used for the preparation of sartans, antihypertensive agents that rank among the top blockbuster drugs worldwide (*Angew Chem Int Ed* 2018e).

Perspective

In the next five years we will build upon the success of genomics- and ecology-driven discovery of novel natural products such as antibiotics and antifungal agents. Non-standard producer strains will be investigated with preference. Specifically, we will increase our research on anaerobes, as we have established the genetic tools for genome editing and heterologous expression. In the area of biosynthesis, we plan to focus on rare transformations involving S and N heteroatoms to install pharmacophores. Motivated by the success of the photosplicing method, we will expore more pharmaceutical applications.

Selected collaborations

Bandow, Julia
Ruhr University Bochum, Germany

Dittmann, Elke
University Potsdam, Germany

Groll, Michael
Technical University Munich, Germany

Kaltenpoth, Martin
Johannes Gutenberg University Mainz, Germany; now Max Planck Institute for Chemical Ecology, Jena, Germany

Pidot, Sacha
University Melbourne, Australia

Stinear, Tim
University of Melbourne, Australia

Watanabe, Kenji
University of Shizuoka, Japan

Wilkinson, Barrie
John Innes Centre, Norwich, Japan

Selected publications

1. Dose B, Ross C, Niehs SP, Scherlach K, Bauer JP, Hertweck C (2020) Food-poisoning bacteria employ a citrate synthase and a type II NRPS to synthesize bolaamphiphilic lipopeptide antibiotics. *Angew Chem Int Ed* 59, 21535-21540.

2. Hermenau R, Ishida K, Gama S, Hoffmann B, Pfeifer-Leeg M, Plass W, Mohr JF, Wichard T, Saluz HP, Hertweck C (2018) Gramibactin is a bacterial siderophore with a diazeniumdiolate ligand system. *Nat Chem Biol* 14, 841-843.

3. Niehs SP, Dose B, Richter S, Pidot SJ, Dahse HM, Stinear TP, Hertweck C (2020) Mining symbionts of spider-transmitted fungus illuminates uncharted biosynthetic pathways to cytotoxic benzolactones. *Angew Chem Int Ed* 59, 7766-7771.

4. Peng H, Ishida K, Sugimoto Y, Jenke-Kodama H, Hertweck C (2019) Emulating evolutionary processes to morph aureothin-type modular polyketide synthases and associated oxygenases. *Nat Commun* 10, 3918.

5. Trottmann F, Franke J, Richter I, Ishida K, Cyrulies M, Dahse HM, Regestein L, Hertweck C (2019) Cyclopropanol warhead in malleicyprol confers virulence of human- and animal-pathogenic *Burkholderia* species. *Angew Chem Int Ed* 58, 14129-14133.

Major third party funding

DFG: Cluster of Excellence Balance of the Microverse

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

DFG: Gottfried Wilhelm Leibniz Prize

BMBF: InfectControl – DrugBioTune

EU: Marie Sklodowska-Curie Actions - Individual Fellowship FUNBIOSIS

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

60 L
55 L
50 L
45 L
40 L
35 L
-34
-31

Department

BIO PILOT PLANT

BIO PILOT PLANT

Mission

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.

Most important results

The following section describes advances and development in the three new focus research areas of the Bio Pilot Plant including a specific outlook towards future developments of these research activities and a general outlook for the development of the department.

New research projects in the focus area of **Bioprocess Intensification** include fundamental research in cultivating amoeba in lab and pilot scale reactor systems (with Hillman group, publication submitted), the formation of mycofactocin for structural anlysis (with Lackner group, *Chem Sci* 2020), bioctalytic formation of Psilocybin (with Hoffmeister group, *Chem Eur J* 2020), spirocompounds formation by *Actinomadura* sp. (with Beemelmans group, *Antibiotics* 2018), the characterization of cyclic lipopeptide productions (*J Biotechnol* 2021) and controlled biotechnological processes with defined microbial co-cultures (*Biotech Biofuels* 2020, *Trends Biotechnol* 2021). This latter is a very hot research field in microbial biotechnology, which will not only provide biotechnological access to complex substrates but also will benefit from microbial share of work and ecological stimulation of product synthesis. With this research plan, we were successful in securing a DFG funded project within the Priority Programm "InterZell". Further, Lars Regestein secured the funding for a research group to perform innovative pressure fermentations (1.200.000 €, Free State of Thuringia with means of the European Social Fund) for challenging new bioprocesses. Specifically, the new team utilizes the new pressure reactor cascade for the formation of natural products with biochemically difficult microbial systems, which are very viscous, tend to strong foam formation and strong catabolic repression. Moreover, anaerobic and anoxic CO_2-consuming bioprocesses is also in the focus of the new sub-group.

With the opening of the new laboratories, the new research area of **Microbial Electrophysiology** was established. Here, biotechnological processes are coupled to electrochemistry to steer and improve the microbial reaction. Thereby, activities go into two directions: i) we investigate and utilize redox-active secreted natural products as electronic link between the microbial metabolism and an electrode to develop new biotechnological reaction routes (*Biotech Bioeng* 2018, *Front Energy Res* 2019, *Front Microbiol* 2019, *ACS Chem Biol* 2020, *Microorganisms* 2020, *Sci Rep* 2021, *Microb Biotechnol* 2021) and ii) we investigate, engineer and utilize CO_2-fixing bacteria for new bioelectrochemical productions (*Front Energy Res* 2018, Agostino, Front Bioeng Biotechnol 2020). The high relevance and innovativeness of this research direction was confirmed by the award of an ERC consolidator grant to Miriam Rosenbaum for the project e-MICROBe, which started in Fall 2020 and participation in the new DFG Priority Programm e-Biotech.

The **Droplet Microfluidic Research** sub-group was very successful in this period with the completion of the PhD theses of Lisa Mahler, Miguel Tovar and Sundar Hengoju, eight published articles (*Sci Rep* 2018, *Biomicrofluidics* 2018, *Anal Bioanal Chem* 2018, *Small* 2019, *Anal Chem* 2019, *Microb Cell Fact* 2020, *Biomicrofluidics* 2020, *eLife* 2021) and several conference awards. The highlights are a publication in the journal *Small*, which was also awarded a 2019 Medac

research award, in which the Bio Pilot Plant and Applied Systems Biology group nicely show how process development and systems biology approaches can benefit each other (*Small* 2019) and a publication in the journal *eLife*, which highlighted the superior power of droplet microfluidics for culturing environmental microbes compared to classical techniques (*eLife* 2021). The former PI, Martin Roth, who retired in September 2018, handed over this sub-group at the peak of its success. The steering and strategic development of this platform from technology development towards application for advanced microbial culturing and screening is now handled by the Chair Miriam Rosenbaum. Previous important members of the group (L. Mahler, M. Tovar) left the Bio Pilot Plant in 2019, but with successful acquisition of new research projects (Cluster of Excellence Balance of the Microverse, LSC InfectoOptics, VersaDrop, Forschungscampus InfectoGnostics and Leibniz Center for Photonics in Infection Biology, LPI), the research capacity of this team was sustained. In future only one team member will focus his research on the technical advancement of the microfluidic platform, while the team works with several local PIs to employ and exploit the platform for very different scientific microbial questions (H. Kries, G. Lackner (both Leibniz-HKI), K. Küsel, K.-U. Totsche (both FSU Jena), F. Bordusa (Uni Halle)).

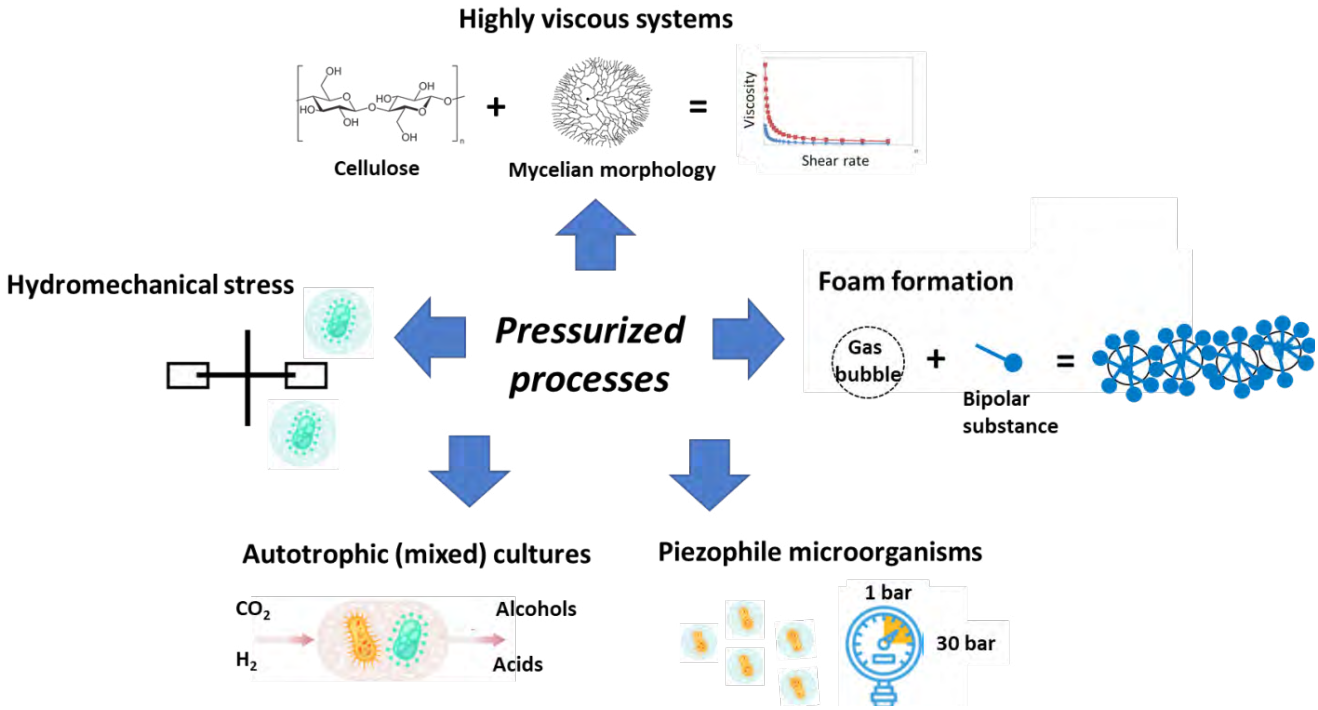


Figure: Main research areas for the new pressurized process conditions beside the known classical high cell density are highly viscous systems, microorganisms susceptible to hydromechanical stress, foaming systems, autotrophic (mixed) cultures, and piezophile microorganisms. Thus, pressure will add several new aspects to the cultivation of microorganisms and the discovery of new natural products.

Perspective

Intrinsically, bioprocess development is a very applied field of research. However, we are building a strategic plan to combine i) state-of-the-art bioprocess

development as a foundation for advanced access to microbial cultures and natural products with ii) the innovative development of new bioprocess strategies like pressure fermentation, ultrahigh throughput droplet cultivations and electrochemically steered bioprocesses. The innovation potential of this department is enormous and has widely been underused in the past decade.

To achieve point i), we already initiated a substantial upgrading and modernization of the Bio Pilot Plant equipment (continuing renewal of 25-year old reactor systems with a replacement of 30 L and 300 L reactors, extension of the portfolio for pressure fermentations, extension of online analysis with off-gas analysis for bioreactors and online analytic for shake flask cultivations). With this, we are not only able to provide a more scientifically grounded support for Leibniz-HKI and external collaborators, but we will also be more proactive in taking on ideas for interesting natural products from collaborating departments to establish and scale highly efficient and fully characterized bioprocesses.

To achieve point ii), we are shifting the focus of our high throughput droplet microfluidic activity from platform development to the application of very challenging microbial cultivations for example in the Cluster of Excellence Balance of the Microverse and innovative microbial experimentation for example at low cell density or for studying cellular evolution. We also provide this platform for research collaborations with other Leibniz-HKI groups (e.g., BDN, CB). As a core strategy, these biological questions will still be complemented by engineers/physicists within the group and from collaborating partners like Leibniz-IPHT and Fraunhofer IOF to further expand on the possibilities of the platform regarding function analysis and droplet handling. At the same time, we will greatly expand our scientific work in the area on microbial electrochemistry with a focus of microbial electrophysiology of mediated extracellular electron transfer. In 2020, an ERC Consolidator Grant started, and Miriam Rosenbaum is a steering group member of the new DFG Priority Program “e-Biotech”.

Overall, the Bio Pilot Plant team is transitioning to a much more scientifically driven work program and will shift from about 1/3 scientists – 2/3 Pilot Plant technicians in 2017 to the opposite ratio 2022.

Selected collaborations

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Wohlleben, Wolfgang
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Ziemert, Nadine
Eberhard Karls University of Tübingen, Germany

Selected publications

1. Askitosari T, Berger C, Tiso T, Harnisch F, Blank L, Rosenbaum M (2020) Coupling an electroactive *Pseudomonas putida* 2 KT2440 with bioelectrochemical rhamnolipid production. *Microorganisms* 8(12), 1959.

2. Askitosari TD, Boto ST, Blank LM, Rosenbaum MA (2019) Boosting heterologous phenazine production in *Pseudomonas putida* KT2440 through the exploration of the natural sequence space. *Front Microbiol* 10, 1990.

3. Schlembach I, Tehrani H, Blank LM, Büchs J, Wierckx N, Regestein L, Rosenbaum M (2020) Consolidated bioprocessing of cellulose to itaconic acid by a co-culture of *Trichoderma reesei* and *Ustilago maydis*. *Biotechnol Biofuels* 13, 207.

4. Svensson C-M*, Shydkiv O*, Dietrich S, Mahler L, Weber T, Choudhary M, Tovar Mº, Figge MTº**, Roth M** (2018) Coding of experimental conditions in microfluidic droplet assays using colored beads and machine learning supported image analysis. *Small* 15, e1802384. *authors contributed equally; ºcorresponding authors; **authors contributed equally

5. Tovar M, Hengoju S, Weber T, Mahler L, Choudhary M, Becker T, Roth M (2019) One sensor for multiple colors: Fluorescence analysis of microdroplets in microbiological screenings by frequency-division multiplexing. *Anal Chem* 91, 3055-3061.

Major third party funding

EU: ERC Consolidator Grant Energizing microbes with redox mediators for new bioproductions - eMICROBe

DFG: Cluster of Excellence Balance of the Microverse

Free State of Thuringia (ESF): Howi - Mit Hochdruck zu neuen Wirkstoffen

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

Leibniz ScienceCampus InfectoOpics: VersaDrop

Department

INFECTION BIOLOGY

INFECTION BIOLOGY

Mission

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.

Most important results

The department of Infection Biology at the Leibniz-HKI works on the role of complement, a central part of innate immunity, in infection, inflammation and human diseases. In evolution complement has existed for over one billion years and the current challenges are to define how pathogenic yeasts and microbes escape complement control, to find new roles of known complement proteins in the human organism, and to identify new complement functions for well characterized proteins. Our work in infection biology focuses on complement and immune evasion of the human pathogenic yeast *Candida albicans*, of the mold *Aspergillus fumigatus,* and on the characterization of the general evasion strategies used by pathogenic microbes. Defective complement regulation is the cause of many human diseases and the identification of genetic causes and autoimmune factors is relevant to understand disease mechanism and to develop new approaches for diagnosis and for therapy. Infections, which induce immune response and which alter the homeotic complement balance trigger autoimmune disorders, kidney diseases and atherosclerosis. The understanding of basic molecular mechanisms helps to identify new biomarkers relevant for immune diagnostics, to develop new complement therapeutics and furthermore to develop concepts for personalized complement mediated therapies.

The role of fungal and microbial immune escape proteins, with focus on multifunctional microbial moonlighting proteins, was analyzed in *C. albicans* and *A. fumigatus*, for the pathogenic bacteria *Borrelia bavarensis*, *Streptococcus pneumoniae* and for the unicellular parasite *Plasmodium falciparum*. Microbial moonlighting proteins are found at different sites or locations, in the cytoplasm, at the cell surface and the proteins are secreted into the surrounding medium. One major role of these multifunctional proteins when exposed at the surface is the acquisition of human plasma regulators such as Factor H and Plasminogen. In addition, we demonstrated that Pra1, the immune evasion protein of *C. albicans*, acts as protease, which cleaves the human complement protein C3 directly and furthermore inactivates C3 activation fragments generated upon host mediated complement activation. Based on their multitude of action, these proteins have additional roles and also modulate the cellular immune response.

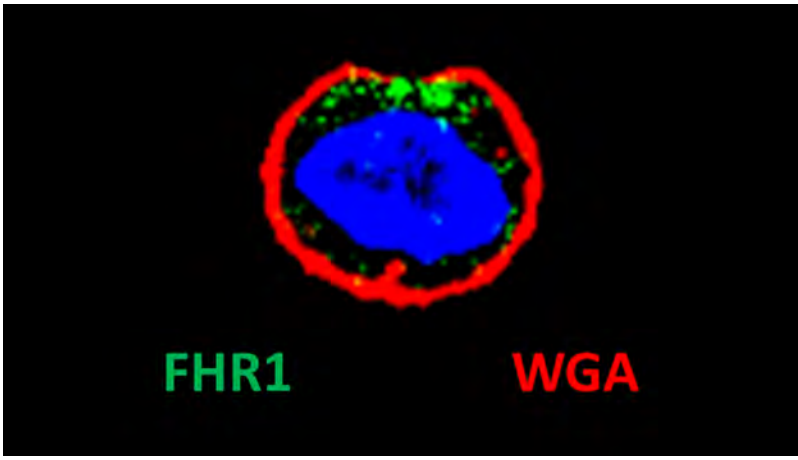

Figure 1: FHR1 binds to sites of membrane damage. Necrotic human monocytes when stained with FHR1 (green fluorescence) and WGA (wheat germ agglutinin; red fluorescence) demonstrates FHR1 binding at sites of membrane damage. FHR1 binds to sites where the cellular membrane is ruptured. One ligand formed at such a damaged surface is Malondialdehyde.

The role of complement proteins in particular of Factor H related proteins (FHRs) in human kidney diseases was evaluated. Laminins such as laminin 521 which are exposed in the damaged kidney were identified as new binding ligands of FHR5. Based on the characterization of new gene variants and new forms of autoantibodies recombinant immune regulators were designed which included central functional domains of FHR1 and Factor H (Figure 1). The proteins show an improved complement inhibitory activity and the potential of these new inhibitors as novel therapeutic agents is further evaluated. A new function of the Factor H related protein1 (FHR1) as activator of the monocytic inflammasome at necrotic sites of vasculopathies was identified (Figure 2).

A new technique was developed to detect the complement activating enzymes, C3 and C5 convertase, directly in tissue and which allows to discriminate between the alternative and the classical pathway convertase. This technique improves diagnostics of complement mediated acute and chronic diseases. The Department Infection Biology has filed three patent applications for new biomarkers and for new targets identified and one patent filed together with CSL Behring, Germany was awarded.

In cooperation with two Biotech Companies, Generic Assay and Medipan in Dahlewitz, Germany a commercial test is evaluated and improved which determines and quantifies complement Factor H autoantibodies in autoimmune kidney diseases such as DEAP-HUS (*CFHR1-CFHR3* **de**ficient and **a**utoimmune **p**ositive form of Hemolytic uremic syndrome), C3 Glomerulopathy and Membranous Nephropathy.

In addition, for the well characterized lipid mediator ApoE, a new role in the complement pathway was demonstrated. ApoE forms complexes with the classical pathway component C1q and these ApoE::C1q

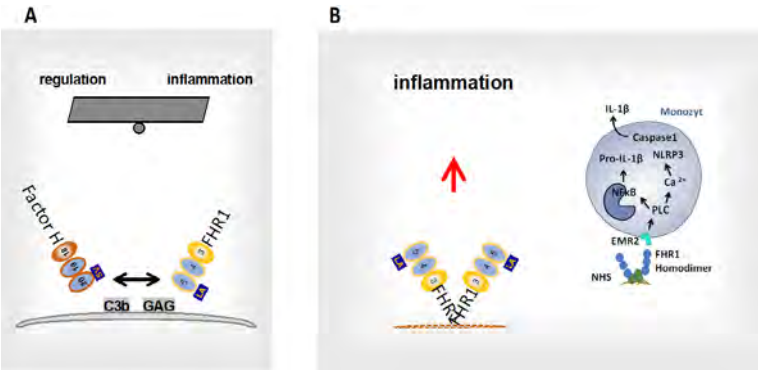

Figure 2: FHR1 has dual immunomodulatory roles. (**A**) FHR1 with the C-terminal region competes with Factor H for binding to C3b and Glycosaminoglycan (GAG) decorated target surfaces. This adjusts the balance of inflammatory FHR1 and of the complement inhibitor Factor H. (**B**) FHR1 as a dimer binds to the surface of necrotic human cells via the N-terminal region. The C-terminus links to monocytes via the EMR2 receptor and induces an inflammatory response.

complexes control classic pathway activation. Deregulated action results in chronic inflammation and in pathology. This new regulatory loop in chronic disorders which is relevant for the pathogenesis of Atherosclerosis and Alzheimer disease and opens new ways for complement mediated therapy of chronic inflammatory complement disorders.

Perspective

Complement is part of innate immunity and forms a central barrier for infectious microbes. Characterizing how human regulators are attached to the microbial surface and the function of such microbial complement binding proteins allows to understand the evasion strategies used by pathogenic microbes. This work focuses mainly on the human pathogenic fungi *C. albicans* and *A. fumigatus* and demonstrates the complexity of specific fungal immune evasion proteins. It furthermore characterizes the sophisticated mechanisms that pathogenic microbes use to control the host immune attack and to survive in an immunocompetent host. The related binding profiles and overlapping functions of such pathogen proteins

reveal common themes of immune evasion, describe strategies for immune evasion of microbial pathogens and identify new targets for therapy.

Elaborating the role of immune mechanisms in human diseases defines new biomarkers and allows to develop assays to score disease severity, to monitor disease progression and to follow the efficacy of a new therapy. Such approaches are relevant for several complement mediated kidney diseases, including C3 glomerulopathy and for common chronic inflammatory diseases, like Atherosclerosis and Alzheimer's disease.

An interesting aspect emerging is that the immune response which is triggered by infectious agents induces inflammation and immune reactions and when not properly controlled and targeted the activation products may also attack and damage intact host tissue and self-cells. Alterations of the underlying genes and of autoimmune factors can deregulate this delicate immune homeostasis and in consequence can result in human diseases and in autoimmunity.

Selected collaborations

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Selected publications

1. Halder LD, Jo EAH, Hasan Z, Gomes MF, Krüger T, Westermann M, Palme DI, Rambach G, Beyersdorf N, Speth C, Jacobsen ID, Kniemeyer O, Jungnickel B, Zipfel PF, Skerka C (2020) *Candida albicans* induces TGF-b transporting vesicles in human monocytes. *Nat Commun* 11, 2331.

2. Irmscher S, Brix SR, Zipfel SLH, Halder LD, Mutlutürk S, Wulf S, Girdaukas E, Reichenspurner H, Stahl RAK, Jungnickel B, Wiech T, Zipfel PF, Skerka C (2019) Serum FHR1 binding to necrotic-type cells activates monocytic inflammasome and marks necrotic sites in vasculopathies. *Nat Commun* 10, 2961

3. Yin C, Ackermann S, Ma Z, Mohanta SK, Li Y, Nietzsche S, Westermann M, Peng L, Hu D, Bontha SV, Srikakulapu P, Beer M, Megens RTA, Steffens S, Markus Hildner M, Eckstein HH, Pelisek J, Herms J, Roeber S, Arzberger T, Habenicht L, Binder CJ, Weber C, Zipfel PF, Skerka C, Habenicht AJR (2018) ApoE attenuates unresolvable inflammation by complex formation with activated C1q. *Nat Med* 25, 496–506.

4. Zecher D, Banas B, Büttner-Herold M, Kirschfink M, Zipfel PF (2018) The Case: A 78-year-old woman with acute kidney injury and hemolytic anemia. *Kid Int* 95, 473-474.

5. Zipfel PF, Wiech T, Stea ED, Skerka C (2020) CFHR gene variations provide insights in the pathogenesis of the kidney diseases atypical hemolytic uremic syndrome and C3 glomerulopathy. *J Am Soc Nephrol* 31, 241-256

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

Greater Cedar Rapids Community Foundation: Kidneeds Fund Role of FHRS in C3 glomerulopathy: Focus on FHR1 and FHR2

PI 10x/23

Department

MICROBIAL PATHOGENICITY MECHANISMS

MICROBIAL PATHOGENICITY MECHANISMS

Mission

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.

Most important results

Our research in the years 2018-2020 has been predominantly characterised by five major lines of inquiry: (1) Role of the peptide toxin candidalysin in *Candida albicans* pathogenicity and host immunity; (2) new models to study *Candida* commensalism and infection, (3) mode of action of new antifungals, (4) immunity to fungal infections, and (5) comparative transcriptomics of infections.

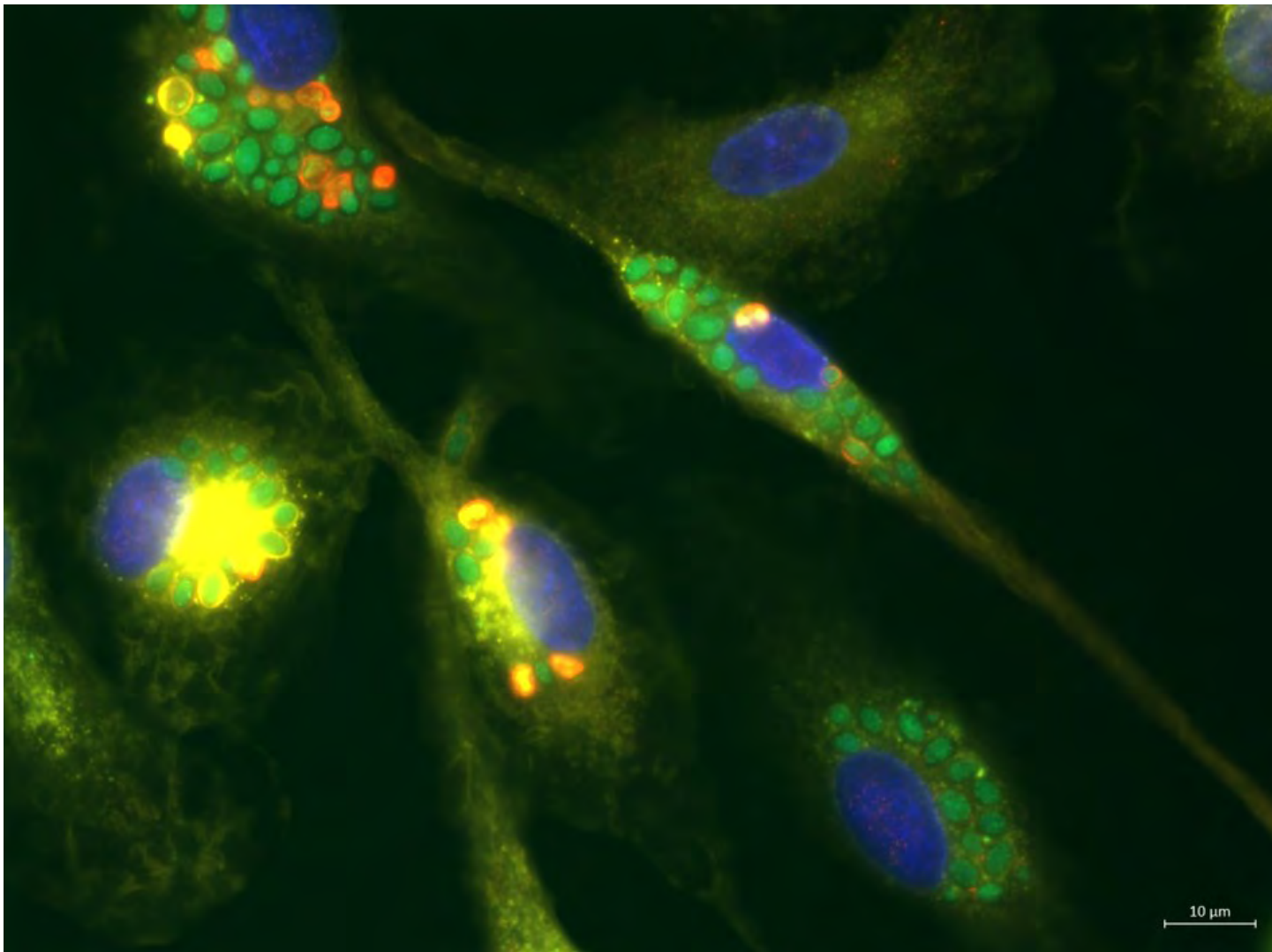
(1) Since the joint discovery of candidalysin by J. Naglik's team at the King's College London and our department (in collaboration with T. Gutsmann, Research Center Borstel; R. Wheeler, Maine; Leibniz-HKI department MAM, Fungal Septomics) (*Nature* 2016), we led or contributed to several follow-up studies to answer multiple questions about the role of this toxin for commensalism and pathogenicity (all collaborations with J. Naglik). For example, we contributed to a study which (i) showed that candidalysin drives epithelial signaling, neutrophil recruitment, and immunopathology during vaginal infections (*Infect Immun* 2018); we (ii) dissected the processing of its precursor polyprotein and its relevance for candidalysin maturation and fungal virulence (with MAM) (*mBio* 2018); and we (iii) showed that candidalysin plays a crucial role during translocation through intestinal barriers (*mBio* 2018). In collaboration with several international partners we also investigated the impact of candidalysin on the immune system and showed that candidalysin (iv) activates the NLRP3 inflammasome and causes cytolysis in phagocytes (*Nat Commun* 2018); (v) mediates neutrophil recruitment during brain infections (*Nat Immunol* 2019); (vi) drives immunity to oral candidiasis (*J Immunol* 2018); (vii) activates innate epithelial immune responses (*Nat Commun* 2019); (viii) is required for neutrophil recruitment and virulence during systemic infections (*J Infect Dis* 2019); (ix) and drives *C. albicans*-Induced allergic airway disease through platelets (*J Allergy Clin Immunol* 2020); furthermore candidalysin (x) promotes alcohol-associated liver disease (*J Hepatol* 2020). We also contributed to two studies which investigated (xi) the regulation of the candidalysin-encoding gene *ECE1* (*mBio* 2020) and (xii) the mechanisms by which phagosome integrity is maintained within macrophages after phagocytosis of *C. albicans* (*Cell Host & Microbe* 2020). This latter work showed that it is rather hyphal extension than candidalysin which causes the phagolysosomal damage.

(2) The intestine is the primary reservoir of *C. albicans* from which systemic infections in immunocompromised patients originate. In this reservoir, the fungus exists as a harmless commensal. However, antibiotic treatment can disturb the microbiota, facilitating fungal overgrowth and favoring pathogenicity. Current *in vitro* gut models for the study of *C. albicans* pathogenesis investigate *C. albicans*'s pathogenic stage rather its commensalism. Within the InfectERA (BMBF-funded) network FunComPath (Role: speaker and PI), we established an *in vitro* gut model that can be used to experimentally dissect commensal-like interactions of *C. albicans* with bacterial microbiota and the host epithelial barrier. We discovered fungal shedding as a novel mechanism by which bacteria contribute to the protection of epithelial surfaces. This article had an associated First Person interview with the joint first authors of the paper (*Dis Model Mech* 2019). Furthermore, in collaboration with A. Mosig, University Hospital Jena, and within the Center of Sepsis Control and Care (CSCC), we con-

tributed to the establishment of a three-dimensional immunocompetent intestine-on-chip model as *in vitro* platform for functional and microbial interaction studies (organ-on-chip) (*Biomaterials* 2019).

(3) One of the highlights in 2019 was a study within a Leibniz-HKI team and in collaboration with the FSU Jena, investigating the mode of action of Jagaricin (*Antimicrob Agents Chemother* 2019). Jagaricin is a lipopeptide produced by the mushroom pathogen *Janthinobacterium agaricidamnosum*, the causative agent of mushroom soft rot disease. Apart from causing lesions in mushrooms, Jagaricin is a potent antifungal active against pathogenic fungi. We showed that Jagaricin acts by impairing membrane integrity, resulting in a rapid flux of ions into susceptible target cells. Accordingly, the calcineurin pathway is required for Jagaricin tolerance in *C. albicans*. Transcriptional profiling of pathogenic yeasts further revealed that Jagaricin triggers cell wall strengthening, general shutdown of membrane potential-driven transport, and the upregulation of lipid transporters, linking cell envelope integrity to Jagaricin action and resistance. Whereas Jagaricin shows hemolytic effects, it exhibited either no or low plant toxicity at concentrations at which the growth of prevalent phytopathogenic fungi is inhibited. Therefore, Jagaricin has a potential for agricultural applications. We see this publication as a flagship publication of the Leibniz-HKI, because (i) it has been performed as a true and very intense collaboration between the

Figure : Swallowed, but alive – *Candida glabrata* survives phagocytosis by macrophages, only few fungi are killed (Marcel Sprenger)



main areas of the Leibniz-HKI – natural products and infection biology. Jagaricin is a natural product discovered in the Leibniz-HKI department BMC with the potential to act as an antimicrobial drug, which was investigated by the department MPM to successfully elucidate the mode of action, supported by the Leibniz-HKI Transfer Group Anti-infectives and the Leibniz-HKI JRG Chemistry of Microbial Communication and by biophysicians of the FSU Jena; (ii) it applies to the motto of the Leibniz Association *theoria cum praxi*: basic research with an applied idea, because it has direct translational aspects, the potential use as a drug against plant pathogens, and finally (iii) it is published in one of the two leading journals for the pharmaceutical industry.

(4) Another highlight in 2019 was a joint publication with P. Bacher and A. Scheffold (University Hospital Schleswig Holstein, Campus Kiel) and with the Leibniz-HKI department MAM. This paper showed the surprising relation between a human anti-fungal protective Th17 response triggered by *C. albicans* in the gut, which causes *Aspergillus fumigatus*-associated immunopathology in the lung. The relevance and induction mechanisms of pathogenic Th17 responses in humans are poorly understood. In this study, we identified *C. albicans* as the major direct inducer of human anti-fungal Th17 cells with cross-reactivity to other fungi, which can be exacerbated by intestinal inflammation. Strikingly, Th17 cells cross-reactive to the airborne fungus *A. fumigatus* are selectively activated

and expanded in patients with airway inflammation, especially during acute allergic bronchopulmonary aspergillosis. We thereby identified heterologous immunity to a single, ubiquitous member of the microbiota as a central mechanism for systemic induction of human anti-fungal Th17 responses and as a potential risk factor for pulmonary inflammatory diseases (*Cell* 2019).

(5) Finally, together with systems biologists of the Leibniz-HKI group SBI we also performed comparative transcriptomics during *ex vivo* blood infection of the most important *Candida* species. The species responsible for > 90% of all *Candida* infections, *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. glabrata* were compared for the first time in a model closely reflecting early stages of blood-borne infections. Our study showed that the individual *Candida* species follow strikingly different strategies in the host, and respond very specific to the diverse stages of blood infections, while the host response to the different *Candida* species was found to be highly conserved (*mBio* 2020).

Our collaborations with the research group of M. Netea (RU Nijmegen) intensified with the arrival of a new postdoc trained in that lab in 2018, funded by an Alexander von Humboldt fellowship. We were involved in demonstrating the role of the NOD2 receptor in modulating the immune response to *A. fumigatus* (*Nat Commun* 2018). In 2019, we collaborated in a project that demonstrated the genetic host signatures that predispose for *C. albicans* bloodstream infections (*J Infect Dis* 2019). Similarly, SIGLEC15 – a key molecule in the recognition of silialic acids – was identified as a major player in defence against recurrent vulvovaginal candidiasis (*Sci Transl Med* 2019). We were also involved in the supervision of a PhD student of M. Netea, who worked on a project aimed at investigating how severe inflammation during sepsis influences the metabolism of circulating monocytes. We demonstrated that endotoxin infusion results in drastic metabolic changes in monocytes that are associated with their immunotolerant phenotype. These metabolic changes were associated with a drastic impact on the interactions with *C. albicans* (*J Leukoc Biol* 2019).

Perspective

Future projects will continue to deal with the *C. albicans* toxin candidalysin and its crucial roles in many aspects of *C. albicans*-host interactions. In this context, we currently have several ongoing projects in collaboration with J. Naglik's team. This also includes a project to elucidate the role of the non-candidalysin Ece1 peptides funded by the DFG. Further future projects are defined by recently secured external funding.

For example, we have received external funding from the European Union, including the FunHoMic ITN *Deciphering fungus-host-microbiota interplay to improve the management of fungal infections*, the HDM-Fun Cluster *Host directed medicine in invasive fungal infections*, and the ANR/BMBF AReST consortium *Antifungal resistance: From surveillance to treatment*. The FunHoMic kick-off meeting was organised by our department at the Leibniz-HKI. Another international collaboration with S. Coulthurst (Dundee) has been initiated together with the Leibniz-HKI group MI, based on a publication by the Coulthurst laboratory in *Nature Microbiology* 2018 which was accompanied by an Editorial written by us (*Nat Microbiol* 2018). This project is funded by the Wellcome Trust and deals with the interaction of bacteria (in particular *Serratia* spp.) with fungi and the bacterial potential to damage fungal cells *via* injection of antifungal effector proteins. Finally, we will continue to contribute to the Cluster of Excellence Balance of the Microverse of the FSU Jena (Role: Coordinator of

Research Area B, core writing team) and will work in an interdisciplinary team on an organ-on-chip model to model diverse aspects of fungal commensalism and pathogenicity. In the DFG TR/CRC 124/2 *Pathogenic fungi and their human host – networks of interaction* FungiNet (Role: Steering committee, Leader Part C, PI Project C1) we will focus on the molecular characterisation of *C. albicans* mucosal colonisation, infection, and translocation.

Selected collaborations

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University of Toronto, Canada

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Kaplan, Daniel
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Selected publications

1. Allert S*, Förster TM*, Svensson CM, Richardson JP, Pawlik T, Hebecker B, Rudolphi S, Juraschitz M, Schaller M, Blagojevic M, Morschhäuser J, Figge MT, Jacobsen ID, Naglik JR, Kasper L, Mogavero S, Hube B (2018) *Candida albicans*-induced epithelial damage mediates translocation through intestinal barriers. *mBio* 9, e00915-18. *authors contributed equally

2. Drummond RA, Swamydas M, Oikonomou V, Zhai B, Dambuza IM, Schaefer BC, Bohrer AC, Mayer-Barber KD, Lira SA, Iwakura Y, Filler SG, Brown GD, Hube B, Naglik JR, Hohl TM, Lionakis MS (2019) CARD9+ microglia promote antifungal immunity via IL-1β- and CXCL1-mediated neutrophil recruitment. *Nat Immunol* 20, 559-570.

3. Fischer D, Gessner G, Fill TP, Barnett R, Tron K, Dornblut K, Kloss F, Stallforth P, Hube B, Heinemann SH, Hertweck C, Scherlach K, Brunke S (2019) Disruption of membrane integrity by the bacteria-derived antifungal jagaricin. *Antimicrob Agents Chemother* 63, pii: e00707-19.

4. Kämmer P, McNamara S, Wolf T, Conrad T, Allert S, Gerwien F, Hünniger K, Kurzai O, Guthke R, Hube B, Linde J, Brunke S (2020) Survival strategies of pathogenic *Candida* species in human blood show independent and specific adaptations. *mBio* 11, e02435-20.

5. Kasper L, König A, Koenig PA, Gresnigt MS, Westman J, Drummond RA, Lionakis MS, Groß O, Ruland J, Naglik JR, Hube B (2018) The fungal peptide toxin Candidalysin activates the NLRP3 inflammasome and causes cytolysis in mononuclear phagocytes. *Nat Commun* 9, 4260.

Major third party funding

DFG: Cluster of Excellence Balance of the Microverse

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

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

EU: Marie-Skłodowska-Curie Innovative Training Network FunHoMic – Deciphering the fungus-host-microbiota interplay to improve the management of fungal infections

EU: Research and Innovation Action HDM-Fun – Host directed medicine in invasive fungal infection

BMBF/ANR: AReST – Antifungal Resistance: From Surveillance to Treatment

LEIBNIZ-HKI

Department

MOLECULAR AND APPLIED MICROBIOLOGY

MOLECULAR AND APPLIED MICROBIOLOGY

Mission

Our department investigates the infection biology of the human-pathogenic fungus *Aspergillus fumigatus* and natural products from filamentous fungi. The aim of our research is to better understand the host-pathogen interplay and to elucidate the role of natural products as mediators of microbial communication.

Most important results

In the field of infection biology, our goal is to gain a better understanding of host-pathogen interactions and to improve diagnosis and therapy of fungal infections. Research on natural products is driven by the elucidation of the ecological function of natural products in microbial communication processes and thereby to understand functional microbial interactions in microbiomes and to discover and improve novel bioactive compounds.

Infection biology of *Aspergillus fumigatus* – Host-pathogen interactions

Research on infection biology focuses on the identification of virulence determinants of *A. fumigatus* and on the characterization of fungal and human factors involved in the cross-talk of the pathogen with human host cells. In a joint effort with the Manchester Fungal Infection Group, we are currently generating a genome-wide *A. fumigatus* gene deletion library as a unique tool for the functional analysis of the *A. fumigatus* genome, including genes that contribute to the pathogenic potential of this fungus (*Curr Protoc Microbiol* 2019). Further, we successfully applied the yeast two-hybrid technology to reveal functions of *A. fumigatus* proteins (*Curr Genet* 2019), and we used a redox proteomics method to reveal increased levels of protein cysteine oxidation under low oxygen levels (*Proteomics* 2019). In collaboration with the group of David S. Perlin (New Jersey, USA) we discovered a novel mechanism of resistance against the antifungal compound caspofungin (*mBio* 2019). In the area of antifungal therapy, we have been working on the encapsulation of antifungal drugs in nanocarriers as promising alternative to traditional formulations of anti-infectives. In close collaboration with the Laboratory of Organic and Macromolecular Chemistry in Jena we succeeded in producing caspofungin functionalised polymethacrylates with antifungal properties (*Biomacromolecules* 2020).

Dihydroxynaphthalene (DHN)-melanin is a natural product that covers dormant conidia of *A. fumigatus*. Previously, we showed that it plays an important role in the virulence of *A. fumigatus* by protecting conidia from the adverse environment of a phagolysosome. In collaboration with Georgios Chamilos (Greece) we uncovered more details about this process. We showed that melanin sequesters Ca^{2+} ions inside the phagosome of macrophages, which abrogates calcium-calmodulin signalling and prevents LC3-associated phagocytosis (*Cell Host Microbe* 2016; *Nat Microbiol* 2018). After establishment of a purification strategy of phagosomes based on magnetic labelling, proteome analysis of conidia-containing phagolysosomes revealed a previously unreported reprogramming of energy metabolism and reduced vATPase assembly on phagolysosomal membranes of macrophages by *A. fumigatus* conidia (*Mol Cell Proteomics* 2018). We further contributed to the discovery of a new C-type lectin receptor, designated as MelLec that recognizes DHN-melanin and plays an important role in controlling invasive *A. fumigatus* infections in mice (*Nature* 2018). Ongoing research has led to the discovery that conidial DHN-melanin deregulates flotillin-dependent lipid rafts in phagolysosomal mem-

branes. This novel molecular mechanism explains the reduced vATPase assembly on phagolysosomal membranes surrounding melanised conidia (*Cell Rep 2020*).

to the innate immune system, less is known about the adaptive immune response to fungal infections. In a joint project with Alexander Scheffold (University of Kiel) and Bernhard Hube (Leibniz-HKI) we identi-

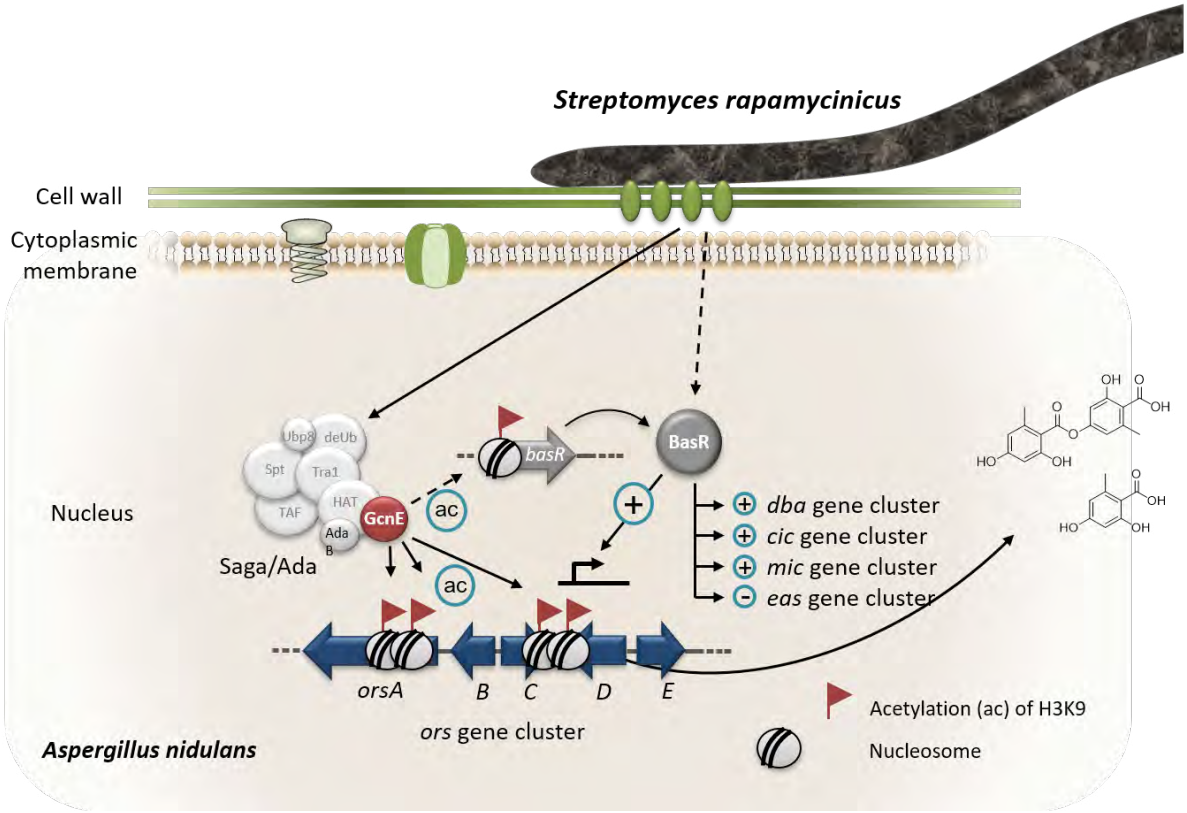

Figure: Criss-cross interkingdom regulation of natural product biosyntheses. Interaction of *Streptomyces rapamycinicus* and *Aspergillus nidulans*. Co-cultivation leads to activation of the *basR* gene. The lysine acetyltransferase GcnE specifically acetylates (ac) lysine (K)9 of histone H3 at the *ors* gene cluster and presumably at the *basR* gene promoter. As a consequence, *basR* is expressed. The transcription factor BasR activates (+) and represses (–) the expression of the *ors*, *cic*, microperfuranone (*mic*) and *eas* gene clusters directly or indirectly (Fischer *et al.*, *eLife* 2018).

Besides melanin, conidial surface proteins also play a role during the initial contact of the fungus with the host immune system. An extensive cell surface proteome profiling by different methods allowed us to define putative targets for the diagnosis and immunotheraphy (*mSphere* 2020; *J Proteome Res* 2020) and led to the discovery of the highly abundant, surface-exposed protein CcpA. It is required for full virulence due to a structural function impacting conidial immunogenicity (*mBio* 2018). In comparison

fied the yeast *Candida albicans* as the main driver of the Th17 response against fungi in humans. Th17 cells directed against other fungi, including *A. fumigatus*, are induced almost exclusively by cross-reactivity to *C. albicans* (*Cell* 2019).

A rapidly developing field in MAM is work on extracellular vesicles produced by neutrophils, macrophages, and epithelial cells in response to *A. fumigatus* (*mBio* 2020). This way we might have discovered

an important contributor to fungicidal activity of human neutrophils against *A. fumigatus*. Moreover, we contributed to develop novel diagnostic procedures based on UV Raman spectroscopy (*Anal Chem* 2018, *J Biophotonics* 2020) and the development of novel antifungal therapies.

Eukaryotic transcription factors and signal transduction involved in iron homeostasis and required for virulence

Transcription factors have long been recognized as critical proteins for *A. fumigatus* pathogenicity, in particular those which are involved in the regulation of iron metabolism. The bZIP regulator HapX is the major regulator of iron homeostasis and also regulates the biosynthesis of siderophores in *A. fumigatus*. Using a co-immunoprecipitation approach and additional genetic experiments we demonstrated that HapX requires the interaction with the monothiol glutaredoxin GrxD for iron sensing (*PLoS Genet* 2019). This study revealed a new important factor in the regulatory circuit of iron homeostasis. Genetic and biochemical analyses (ChIP-seq, surface plasmon resonance) identified DNA motifs recognised by HapX together with the CCAAT-binding complex (CBC) and revealed a surprising plasticity of HapX:CBC:DNA interaction (*Nucleid Acis Res* 2020).

Natural products as chemical language for microbial communication and as basis for therapeutics

We hypothesize that the biological role of many natural products is to mediate microbial communication. Previously, we discovered that the intimate physical contact between the Gram-positive bacterium *Streptomyces rapamycinicus* with the filamentous fungus *Aspergillus nidulans* leads to the activation of silent natural product biosynthetic gene clusters in the fungus (*PNAS* 2009). Our work showed that this phenomenon is triggered by chromatin modifications, in particular by histone H3 acetylation. These findings led to the novel concept that bacteria are able to manipulate the chromatin modification machinery of eukaryotes (*Proc Natl Acad Sci* 2011). A genome-wide ChIP-seq analysis revealed differentially acetylated histones in the region of genes involved in natural product production. The Myb-like transcription factor BasR was discovered that is highly induced upon interaction with *S. rapamycinicus* and was shown to be important for the regulation of natural product gene clusters. Our findings also provide the first example to predict microbial interaction partners based on their genetic inventory (*eLife* 2018). Besides further analysing the molecular mechanisms of the interaction between *S. rapamycinicus*/ *Streptomyces iranensis* and *A. nidulans*, we try to establish targeted (ecological) induction of the production of such natural products that are directed against the inducing microorganism. Further, we have expanded this bipartite system to a tripartite system, comprising the filamentous fungus *A. nidulans*, the unicellular green algae *Chlamydomonas reinhardtii* and the Gram-positive bacterium *S. iranensis*. Genetic analyses and matrix-assisted laser desorption/ ionization mass spectrometry imaging demonstrated that *S. iranensis* secretes the algicidal compound azalomycin F upon contact with *C. reinhardtii*. As a counter-measure, *A. nidulans* forms a lichen-like association upon which *C. reinhardtii* cells embedded in the fungal mycelium are protected from azalomycin F. These findings reveal a strategy whereby algae survive lethal environmental algicides through cooperation with fungi. This strategy may represent a mutual selection advantage leading to the formation of lichens (*ISME J* 2020).

In all these projects on natural products, we have improved genetic engineering technologies (synthetic biology), such as the advanced CRISPR/Cas9 systems (ASC *Synth Biol* 2017), and the production of polycistronic mRNA in fungi for the production of novel compounds, such as new derivatives of the insecticide austinoid (*ACS Chem Biol* 2017, *Metab Eng* 2018).

Perspectives

In the next years we will address the research goals formulated in the various CRC / Excellence / BMBF / EU programs. In this context, our future research aims at studying the abiotic and biotic factors that impact *A. fumigatus* pathobiology. We have an ongoing program on the mechanisms forming phagolysosomes in macrophages, disturbance of their activity by DHN melanin, the importance and formation of flotillin-dependent lipid rafts in this process, and the use of nanoparticles loaded with antifungal agents to target pathogen-containing phagolysosomes for therapy. Another major research area is devoted to extracellular vesicles in immune cells, their formation, their localization in pathogens *e.g.* intracellularly, and the targeting mechanisms. A new research area focuses on functional microbiome analyses.

Research on natural products will be further devoted to their biosynthesis and in particular to the elucida-

tion of their ecological function in communication processes in complex systems. This also includes the discovery of novel bioactive compounds, the identification of their mode of action in particular on fungi and their modification and production by molecular biotechnology.

Selected collaborations

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Selected publications

1. Bacher P, Hohnstein T, Beerbaum E, Röcker M, Blango MG, Kaufmann S, Röhmel J, Eschenhagen P, Grehn C, Seidel K, Rickerts V, Lozza L, Stervbo U, Nienen M, Babel N, Milleck J, Assenmacher M, Cornely OA, Ziegler M, Wisplinghoff H, Heine G, Worm M, Siegmund B, Maul J, Creutz P, Tabeling C, Ruwwe-Glösenkamp C, Sander LE, Knosalla C, Brunke S, Hube B, Kniemeyer O, Brakhage AA, Schwarz C, Scheffold A (2019) Human anti-fungal Th17 immunity and pathology rely on cross-reactivity against *Candida albicans*. *Cell* 176, 1340-1355.e15.

2. Fischer J, Müller SY, Netzker T, Jäger N, Gacek-Matthews A, Scherlach K, Stroe MC, García-Altares M, Pezzinic F, Schoeler H, Reichelt M, Gershenzon J, Krespach MKC, Shelest E, Schroeckh V, Valiante V, Heinzel T, Hertweck C, Strauss J, Brakhage AA (2018) Chromatin mapping identifies BasR, a key regulator of bacteria-triggered production of fungal secondary metabolites. *eLife* 7, pii: e40969.

3. Furukawa T, Scheven MT, Misslinger M, Zhao C, Hoefgen S, Gsaller F, Lau J, Jöchl C, Donaldson I, Valiante V, Brakhage AA, Bromley MJ, Haas H, Hortschansky P (2020) The fungal CCAAT-binding complex and HapX display highly variable but evolutionary conserved synergetic promoter-specific DNA recognition. *Nucleic Acids Res* 48, 3567-3590.

4. Krespach MKC, García-Altares M, Flak M, Schoeler H, Scherlach K, Netzker T, Schmalzl A, Mattern DJ, Schroeckh V, Komor AJ, Mittag M, Hertweck C, Brakhage AA (2020) Lichen-like association of *Chlamydomonas reinhardtii* and *Aspergillus nidulans* protects algal cells from bacteria. *ISME J* 14, 2794-2805.

5. Schmidt F, Thywißen A, Goldmann M, Cunha C, Cseresnyés Z, Schmidt H, Rafiq M, Galiani S, Gräler MH, Chamilos G, Lacerda JF, Campos Jr A, Eggeling C, Figge MT, Heinekamp T, Filler SG, Carvalho A, Brakhage AA (2020) Flotillin-dependent lipid-raft microdomains are required for functional phagolysosomes against fungal infections. *Cell Reports* 32, 108017.

Major third party funding

DFG: Cluster of Excellence Balance of the Microverse

DFG: CRC 1127 ChemBioSys – Project B02

DFG: CRC/TR 124 FungiNet – Project A1, Z1 and Z2

DFG CRC 1278 PolyTarget – Project B02

DFG: Excellence Graduate School Jena School of Microbial Communication

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

BMBF: Zwanzig20 – Partnerschaft für Innovation Consortium InfectControl – New anti-infection strategies

EU: Research and Innovation Action HDM-Fun – Host directed medicine in invasive fungal infection

BMBF/ANR: AReST – Antifungal Resistance: From Surveillance to Treatment

LEIBNIZ-HKI

Department

PALEOBIOTECHNOLOGY

(until 31.12.2019: Junior Research Group Chemistry of Microbial Communication)

PALEOBIOTECHNOLOGY

Mission

The mission of this research group is to identify novel natural products from interacting microbes, in particular bacteria and their predators as well as ancient microbiomes. We elucidate the structure of the metabolites and identify their biosyntheses, biological activity, and ecological function.

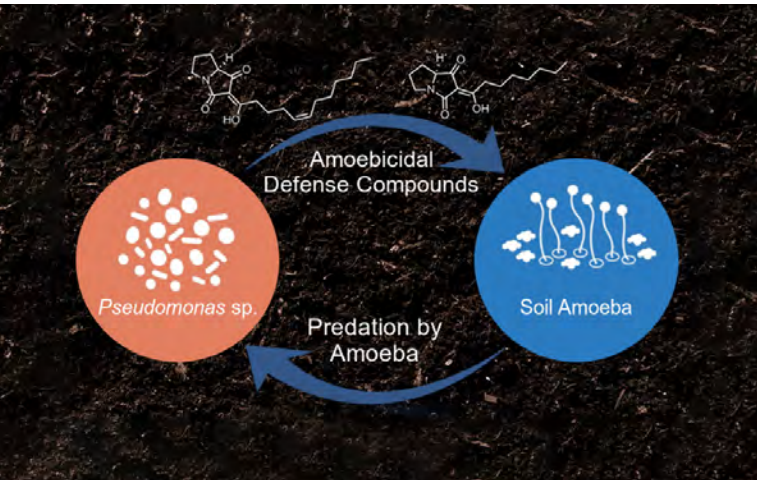

Figure: Soil bacteria are constantly threatened by various predators. Some bacteria can defend themselves via the secretion of natural products with anti-predator activity.

Most important results

In 2020, the new Department Paleobiotechnology was established with funding by the Werner Siemens Foundation. The main focus lies on the isolation of new, microbially produced bioactive molecules. We perform in-depth structure elucidation, mode of action, biosynthesis, and evolutionary studies. The natural products are obtained from ancient sources of microbial DNA as well as from interacting microorganisms. Funding from the Werner Siemens Foundation was obtained to investigate the isolation and production of natural products from ancient sources in collaboration with the group of Christina Warinner (MPI Evolutionary Anthropology, Leipzig and Harvard University). A potent bioinformatics platform was established to assemble ancient DNA sequences and identify biosynthetic genes as well as antibiotic resistance genes. Candidate clusters were commercially synthesized and heterologous expression systems are currently being established. Additionally, bacterial samples from ancient bone material as well as from traditionally fermented Mongolian dairy products were isolated and characterized. Natural product producers could be isolated and the effects of these natural products on the preservation of bones and on fermented dairy products is currently being investigated.

In addition to 'ancient' natural products, our group focuses on natural products from pseudomonads that are part of interacting microbial associations. Antagonistic predator–prey associations have been shown to be particularly rich in bioactive secondary metabolites.

We thus identified a novel nonribosomal peptide, jessenipeptin, which is produced by a *Pseudomonas* strain. Interestingly, this strain also produces mupirocin, a polyketide natural product, which is used as topical antibiotic. We could demonstrate, that both compounds are co-secreted and show a strong synergistic activity against the human pathogen, methicillin-resistant *Staphylococcus aureus*, MRSA (*PNAS* 2018). For structure elucidation and bioactivity testing of these compounds, we collaborated with the Leibniz-HKI Bio Pilot Plant. Interestingly, the producing organism also secreted novel lipo-octapeptides, the virginiafactins. In collaboration with the Junior Research Groups of Gerald Lackner and Hajo Kries, we were able to make use of this *Pseudomonas* strain to retrace the evolutionary diversification of nonribosomal peptides (*Chem Sci* 2019).

We were able to identify a novel form of cooperative bacterial defense. A systematic analysis of binary

combinations of co-isolated bacteria revealed strains that were individually susceptible to predation, but together killed their predator. This cooperative defense relies on a *Pseudomonas* species producing syringafactin, a lipopeptide, which induces the production of peptidases in a *Paenibacillus* strain. These peptidases then degrade the innocuous syringafactin into compounds, which kill the predator. A combination of bio-prospecting, co-culture experiments, genome modification, and transcriptomics unravel this novel natural product-based defense strategy (*PNAS* 2020). We also used structuring element (*i.e.* non-homogeneous media) to investigate these microbial predator–prey interactions in more complex environments. A combination of staining (FISH) and microscopy enabled us to shed light on these associations.

In previous studies of amoebae-bacteria interactions, we had isolated pyreudione alkaloids (*Angew Chem Int Ed* 2017). We were able to elucidate their biosynthesis and performed phylogenetic analysis to understand the evolutionary history regarding the cyclisation mechanism in pyreudione biosynthesis (*Cell Chem Biol* 2018). Recently, we could show in collaboration with the group of Oliver Werz (FSU Jena) that the mode of action of these compounds is based on their protonophore activity. A structure-activity-relationship study as well as biochemical essays were required to identify this mode of action (*ACS Chem Biol* 2019). Currently, we are investigating the particular aspect of the pyreudione biosynthesis, namely the lipoinitiation step. This study would be applicable to most of the pseudomonal lipopeptides

and allow to understand how nonribosomal peptide synthetases can differentiate between different lipid starter moieties.

Our amoebae–bacteria 'platform' also allowed for the identification of novel butenolides (the styrolides) from a *Pseudomonas* strain. We elucidated their structures, performed a chemical synthesis, and propose a biosynthesis based on the analysis of gene KO mutants. A transcriptomic analysis between the producer and a mutant that does not produce the styrolides allowed to infer about a putative role as signal molecule (*Angew Chem Int Ed* 2020).

We also developed a new strategy to activate silent biosynthetic gene clusters in *Pseudomonas* species that relies on the generation of chimeric LuxR-type transcription factors. Thus, we could identify and isolate the novel natural product pseudmonol (*Angew Chem Int Ed* 2020).

Currently, several projects are ongoing that investigate the roles of bacterial cyclic lipopeptides in microbial interactions. We were able to isolate and characterize novel lipopeptides with potent bioactivities. Two reviews were published that provide a comprehensive account on lipopeptides produced by pseudomonads (*Nat Prod Rep* 2020) and on the methods to elucidate their structures (*Org Biomol Chem* 2020).

Whereas most of our attention is spent on the bacterial side of the predator–prey association, we are also investigating the amoebal side. We could establish the CRISPR-Cas9 system in amoeba and we are interested in the role of signal molecules for intraspecies communication. In collaboration with Thomas Winckler (FSU Jena), we were able to shed light on the glorin-based signal systems (*ACS Chem Biol* 2018 and *Beilstein J Org Chem* 2018). Currently, there is ongoing work on deciphering the structures and roles of polyketides of the social amoeba *Dictyostelium discoideum* using CRISPR-Cas9 as well as understanding the glorin-based aggregation system in social amoebae (DFG STA1431/3-1). These projects are done in collaboration with Falk Hillmann (Leibniz-HKI) and Thomas Winckler (FSU Jena), respectively.

Selected collaborations

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Selected publications

1. Arp J, Götze S, Mukherji R, Mattern DJ, Garcia-Altares M, Klapper M, Brock DA, Brakhage AA, Strassmann JE, Queller DC, Bardl B, Willing K, Peschel G, Stallforth P (2018) Synergistic activity of co-secreted natural products from amoebae-associated bacteria. *Proc Natl Acad Sci USA* 115, 3758-3763.

2. Götze S, Arp J, Lackner G, Zhang S, Kries H, Klapper M, García-Altares M, Willing K, Günther M, Stallforth P (2019) Structure elucidation of the syringafactin lipopeptides provides insight in the evolution of nonribosomal peptide synthetases. *Chem Sci* 10, 10979-10990.

3. Klapper M, Braga D, Lackner G, Herbst R, Stallforth P (2018) Bacterial alkaloid biosynthesis: Structural diversity via a minimalistic nonribosomal peptide synthetase. *Cell Chem Biol* 25, 659-665.

4. Klapper M, Schlabach K, Paschold A, Zhang S, Chowdhury S, Menzel KD, Rosenbaum MA, Stallforth P (2020) Biosynthesis of pseudomonas-derived butenolides. *Angew Chem Int Ed* 59, 5607-5610

5. Mukherji R, Zhang S, Chowdhury S, Stallforth P (2020) Chimeric LuxR transcription factors rewire natural product regulation. *Angew Chem Int Ed* 59, 6192-6195.

Major third party funding

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

DFG: SMABI – Sekundärmetabolite in Amöben-Bakterien Interaktionen

DFG: Sigmosa – Glorin signaling during the multicellular development of social amoebae

Werner Siemens Foundation: Paleobiotechnology

Boehringer Ingelheim Foundation: Identification of Microbially Produced Amoebicides

Research Group

APPLIED SYSTEMS BIOLOGY

APPLIED SYSTEMS BIOLOGY

Mission

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.

Most important results

During the reporting period 2018-2020, the research group ASB contributed to both Leibniz-HKI research foci – *natural product research* and *infection biology* – in various ways.

In collaboration with the microfluidics subgroup at the Bio Pilot Plant, we developed a method to encode different experimental conditions in picoliter-droplets based on the co-encapsulation of biological samples with colored polystyrene beads. The decoding of the droplets, as well as their content quantification and the droplet sorting, are performed by machine learning supported analysis of triggered microscopy images of individual droplets in flow. A correct classification of 99.6% of droplets to their experimental conditions was achieved by combining bead classification using a random forest classifier and Bayesian inference (*Small* 2019). Thus, the realization of image-based technical requirements for microfluidic ultra-high throughput approaches now enables exploring the biodiversity in the microbial world as a practically inexhaustible source of naturally selected bioactive compounds. This research will be continued within project *AutoScreen* that is funded by the European Regional Development Fund and the State of Thuringia (2017-2020).

Studying host-pathogen interactions is also realized using confrontation assays monitored by imaging endpoint experiments or by live cell imaging. Algorithms for the automated analysis of both types of image data have been developed in the ASB in collaboration with the department MAM for the confrontation between alveolar macrophages and *Aspergillus fumigatus* conidia and with the research group Fungal Septomics for the confrontation between neutrophils with *Candida albicans* or *C. glabrata*. We developed the algorithm for migration and interaction tracking (AMIT) applying machine learning methods for the enhanced recognition of whole cell tracks (*Sci Rep* 2019) and the algorithm for confrontation assay quantification (ACAQ) of label-free cells based on a morphological filter approach (*Cytometry A* 2018). This newly developed version of ACAQ has proven its high potential in various collaborative studies: (i) We performed a comparative analysis of phagocytosis assays confronting 17 worldwide-distributed strains of *Lichtheimia* species with alveolar macrophages. In collaboration with researchers from the Jena Microbial Resource Collection, we found that the phagocytic vulnerability of *Lichtheimia* species depends on their geographical origin, where strains within the same geographic region behave similarly, but strongly differed amongst the regions (*Environ Microbiol* 2019). (ii) We determined the impact of fluorescence labeling on phagocytosis measurements in confrontation assays and found that the phagocytosis of fungal spores by DID-stained macrophages is significantly reduced, whereas the uptake of spores is significantly increased by FITC staining (*Front Microbiol* 2020). (iii) We quantified the reduced capability of alveolar macrophages to phagocytose Lichtheimia corymbifera spores in the presence of antibodies against the macrophage-associated heat-shock family protein Hspa8 (*Environ Microbiol* 2020). (iv) We identified lipid-raft microdomains as essential components of phagolysosomal membranes of macrophages and studied their dependence on flotillin regarding the

ability to phagocytose spores (*Cell Rep* 2020). (v) We quantified the cellular uptake of bio-based nanoparticles functioning as targeted multi-drug containers in the context of inflammation and sepsis (*J Control Rel* 2020). Both algorithms, ACAQ and AMIT, will play central roles in future analyses of microscopy data generated within the CRC 1278 PolyTarget - Polymer-based nanoparticle libraries for anti-inflammatory strategies (2017-2021).

The research group ASB is continuously increasing its portfolio of image analysis methods by extending the analysis for various imaging modalities. For example, in collaboration with the department Infection Biology, analyses of images from laser scanning confocal microscopy (LSCM) were performed in studies of the hemolytic uremic syndrome with regard to quantifying the damage of human endothelial cells mediated by *Streptococcus pneumoniae* (*J Infect Diseases* 2018). Similarly, the impact of immune evasion proteins of *A. fumigatus* that block the host innate immune attack and are involved in the disruption of human lung epithelial cell layers were quantified based on LSCM data (*Front Immunol* 2018). Furthermore, we investigated the mechanisms on how *A. fumigatus* evades the innate immune attack and identified *A. fumigatus* enolase, AfEno1, a fungal allergen that acts as a surface ligand for human plasma complement regulators. In this context we quantified the impact of *A. fumigatus* conidia on damage of human lung epithelial cells and induction of cell retraction (*Front Immunol* 2019). Various other studies required customized solutions for automated image processing due to a higher system complexity: (i) We quantified the germination and hyphal growth of *C. albicans* from microscopy images to study the role of transcription factor Stp2 regarding biofilm formation and stability (*Front Microbiol* 2020). (ii) We elucidated the antifungal effect of extracellular vesicles released by neutrophils confronted with *Aspergillus fumigatus* by quantifying hyphal growth from time-series image data (*mBio* 2020). (iii) We contributed to a study uncovering C5a signaling as a mediator of immunosuppressive processes and unveiling C5a receptor 1 as therapeutic target in a murine sepsis model (*Mol Therapy* 2020).

Together with collaborators at the Jena University Hospital, intravital LSCM was applied to murine models of infection in order to quantify differences in the hepatic host response to bacterial and fungal infections in terms of hepatic metabolism and liver function (*Theranostics* 2018). Recently, we started to analyze data from whole-organ imaging by light sheet fluorescence microscopy (LSFM) together with collaborators from the University Hospitals in Essen

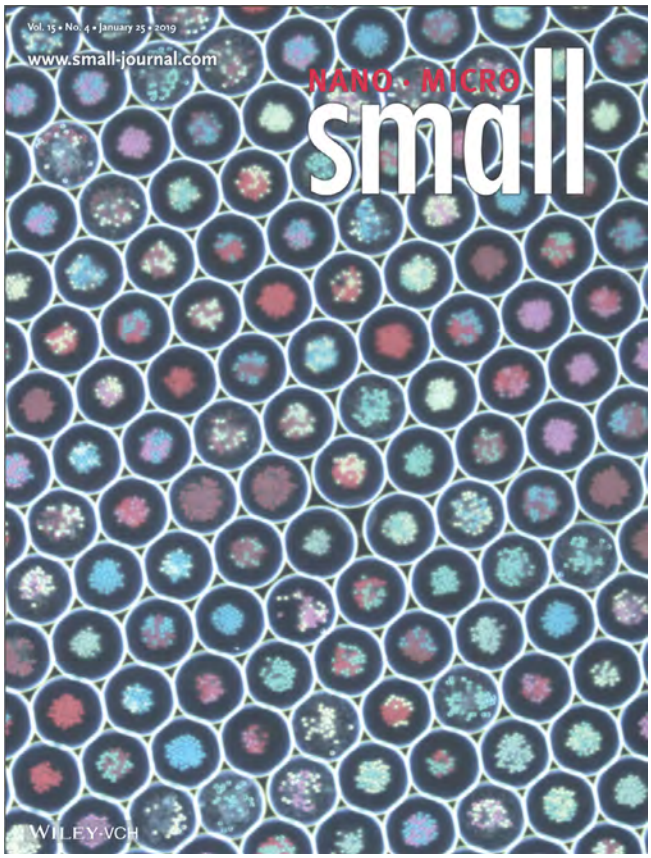

Figure: Encoding of a population of microfluidic pico-liter droplets with colored polystyrene beads for the simultaneous study of multiple experimental conditions. Droplets are imaged using brightfield microscopy and are successfully decoded and evaluated by machine learning supported image analysis. The novel encoding strategy is applied to antibiotic susceptibility testing of droplet-encapsulated *E. coli* bacteria as a proof-of-principle.

and Jena (*Front Immunol* 2018). The terabyte-volume data generated by LSFM poses a special challenge regarding the time-efficient computation of organ features; in the near future, we will focus on developing a significantly improved and extended open-source framework based on the machine-oriented programming language C++.

Furthermore, the research group ASB is leading the development of an analysis platform for microscopy data from a three-dimensional microphysiological model of the human intestine. These so-called gut-on-chip models resemble organotypic microanatomical structures and include tissue resident innate immune cells for functional and microbial interaction studies with spatial resolution (*Biomaterials* 2019). We also established a lung-on-chip model to study the co-infection with *Staphylococcus aureus* after primary influenza virus infection by quantifying the damage of the endothelium (*Biofabrication* 2020) as well as the down-regulation of surfactant protein-A (*Microorganisms* 2020). This analysis platform for microscopy data of organ-on-chip models will be further developed in newly started projects within the Cluster of Excellence Balance of the Microverse and within the Leibniz ScienceCampus InfectoOptics "Combating infectious diseases with advanced optical methods" to study microbial and viral infections in a human lung-on-chip model.

We also advanced our portfolio of theoretical methods: (i) We developed a standardized interface based in C++ for the automated analysis of big volume image data, as routinely generated in whole-organ imaging using lightsheet microscopy (*SoftwareX* 2020). (ii) We also developed a simulation framework for quantifying errors and selecting optimal parameters of image deconvolution (*J Biophotonics* 2020). (iii) We extended the spherical harmonics approach for cell shape classification by accounting for the shape dynamics of migrating cells (*Sci Rep* 2020).

In addition to the portfolio of image analysis methods, a broad range of modeling techniques has been implemented in the ASB. These include state-based modeling (*Front Immunol* 2018) as well as agent-based modeling (*Front Immunol* 2018) to simulate interactions at the molecular and cellular level. For example, within the CRC/TR 124/2 FungiNet - Pathogenic fungi an their human host: Networks of interaction (2017-2021), we performed quantitative simulations to predict treatment strategies against fungal infections in virtual neutropenic patients (VNP). The combined analysis of experiment and computational modeling revealed that a cytokine treatment, which enhances neutrophil activity in terms of phagocytosis and migration, can successfully clear infections by the remaining neutrophils of VNP; and that this treatment is more effective for *C. glabrata* than for *C. albicans*. Moreover, we simulate VNP to investigate possible mechanisms of microbial immune evasion in a comparative fashion and to suggest new whole-blood assays that allow for the validation or rejection of these hypothesized mechanisms. In the context of *A. fumigatus* infections, we developed a hybrid agent-based model for the comparative assessment of aspergillosis in the murine and human lung by virtual infection modeling (*Front Immunol* 2019). Our computer simulations enable comparative quantification of *A. fumigatus* infection clearance in the two hosts to elucidate (i) the complex interplay between the alveolar morphometry and the fungal burden and (ii) the dynamics of infection clearance, which for realistic fungal burdens is found to be more efficiently realized in mice compared to humans. Based on data from the lung-on-chip model, realistic parameters can be used in spatiotemporal models of lung infections with *A. fumigatus* (*Front Microbiol* 2020).

Selected collaborations

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Selected publications

1. Hassan MIA, Cseresnyes Z, Al-Zaben N, Dahse HM, Vilela de Oliveira RJ, Walther G, Voigt K, Figge MT (2019) The geographical region of origin determines the phagocytic vulnerability of *Lichtheimia* strains. *Environ Microbiol* 21, 4563-4581.

2. Gerst R, Medyukhina A, Figge MT (2020) MISA++: A standardized interface for automated bioimage analysis. *SoftwareX* 11, 100405.

3. Medyukhina A*, Blickensdorf M*, Cseresnyés Z, Ruef N, Stein JV, Figge MT; * (2020) Dynamic spherical harmonics approach for shape classification of migrating cells. *Sci Rep* 10(1), 6072. *authors contributed equally

4. Svensson C-M*, Shydkiv O*, Dietrich S, Mahler L, Weber T, Choudhary M, Tovar M°, Figge MT°**, Roth M** (2019) Coding of experimental conditions in microfluidic droplet assays using colored beads and machine learning supported image analysis. *Small* 15, e1802384. *authors contributed equally; °corresponding authors; **authors contributed equally

5. Timme S, Lehnert T, Prauße MTE, Hünniger K, Leonhardt I, Kurzai O, Figge MT (2018) Quantitative simulations predict treatment strategies against fungal infections in virtual neutropenic patients. Front Immunol 9, 667.

Major third party funding

DFG: Cluster of Excellence Balance of the Microverse

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

BMBF: Research Campus Infectognostics

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 AND NATIONAL REFERENCE CENTER FOR INVASIVE FUNGAL INFECTIONS

FUNGAL SEPTOMICS AND NATIONAL REFERENCE CENTER FOR INVASIVE FUNGAL INFECTIONS

Mission

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 are the central contact point for diagnostics and therapy of invasive fungal infections (IFI) in Germany. In addition to targeted consultation and special diagnostic services we share our expertise with our national and international partners.

Most important results

After appointment of Oliver Kurzai as Chair of Medical Microbiology & Mycology at the Julius Maximilians University Würzburg in 2017, the research group Fungal Septomics was restructured as a collaboration between Leibniz-HKI and University Würzburg. As head of the Institute for Hygiene and Microbiology in Würzburg, Oliver Kurzai is responsible for infectious diseases diagnostics at the University Hospital Würzburg as well as for teaching of ~300 MD students per year. In parallel, he is employed as an independent research group leader at the Leibniz-HKI and together with S. Vylkova and B. Hube represents the Leibniz-HKI in the Septomics Research Center, a joint research facility between Leibniz-HKI, University and University Hospital Jena.

General research focus

Worldwide, a continuously growing number of patients are at risk for invasive fungal infections (IFI). At the same time, an increasing variety of fungal species emerges as relevant pathogens and antifungal drug resistance starts to pose a challenge for clinical management of IFI. The FS/NRZMyk group bridges groundbreaking research at the Leibniz-HKI with clinical application and enables direct access of Leibniz-HKI researchers to clinical isolates of pathogenic fungi. In our team, we investigate the interaction between fungal pathogens and the human host, aiming to elucidate virulence mechanisms as well as clinically relevant effector mechanisms in the host immune response. This work relies on intimate cooperation with other groups at the Leibniz-HKI, including bioinformatics (SBI and ASB), as well as the departments MAM and MPM and with international partners. In 2014, Oliver Kurzai has been appointed head of the NRZMyk based at the Leibniz-HKI. After positive evaluations by the Robert Koch Institute and the Federal Ministry for Health, this appointment has been re-newed in 2016 and 2019. Within the NRZMyk, we directly apply our expertise to improve patient care. We provide diagnostic tests beyond the scope of routine diagnostic labs and consiliary advice for treating to physicians and public health authorities. The NRZMyk is the central diagnostic referral center for invasive fungal infections in Germany. Together with national and international partners, we coordinate projects on epidemiology of IFI, emergence of new pathogens and antifungal drug resistance. Furthermore, we engage in education and training of MDs as well as public health services with regard to IFI.

Selected Results 2018-2020

Pathogenicity and Virulence in Fungi

Analysis of fungal virulence determinants has been continued after the structural change in 2017 in close cooperation with other groups at Leibniz-HKI. We have studied filamentation in *C. albicans* - a major virulence factor. In our work, we analyse genetic regulation of the yeast-to-filament transition as well as the role of the quorum sensing molecule farnesol in pathogen-host interaction (*mBio* 2020).

Antifungal Immunity and Genetic Susceptibility

Manifestation of IFI is in most cases based on underlying defects in the host immune response. To address the role of different immune effector mechanisms in the antifungal response we use infection models for primary human immune cells as well as a human whole blood infection model. Besides neutrophils as central players in the immune response against invasive *Candida* and *Aspergillus* infections (*mBio* 2018; *Semin Cell Dev Biol* 2019), we have studied activation patterns in human dendritic cells (*J Immunol* 2019) and natural killer (NK-) cells (*J Inf Dis* 2020). Within the CRC/TR 124 FungiNet and in close collaboration with the ASB group (M. T. Figge), we set up a human whole blood

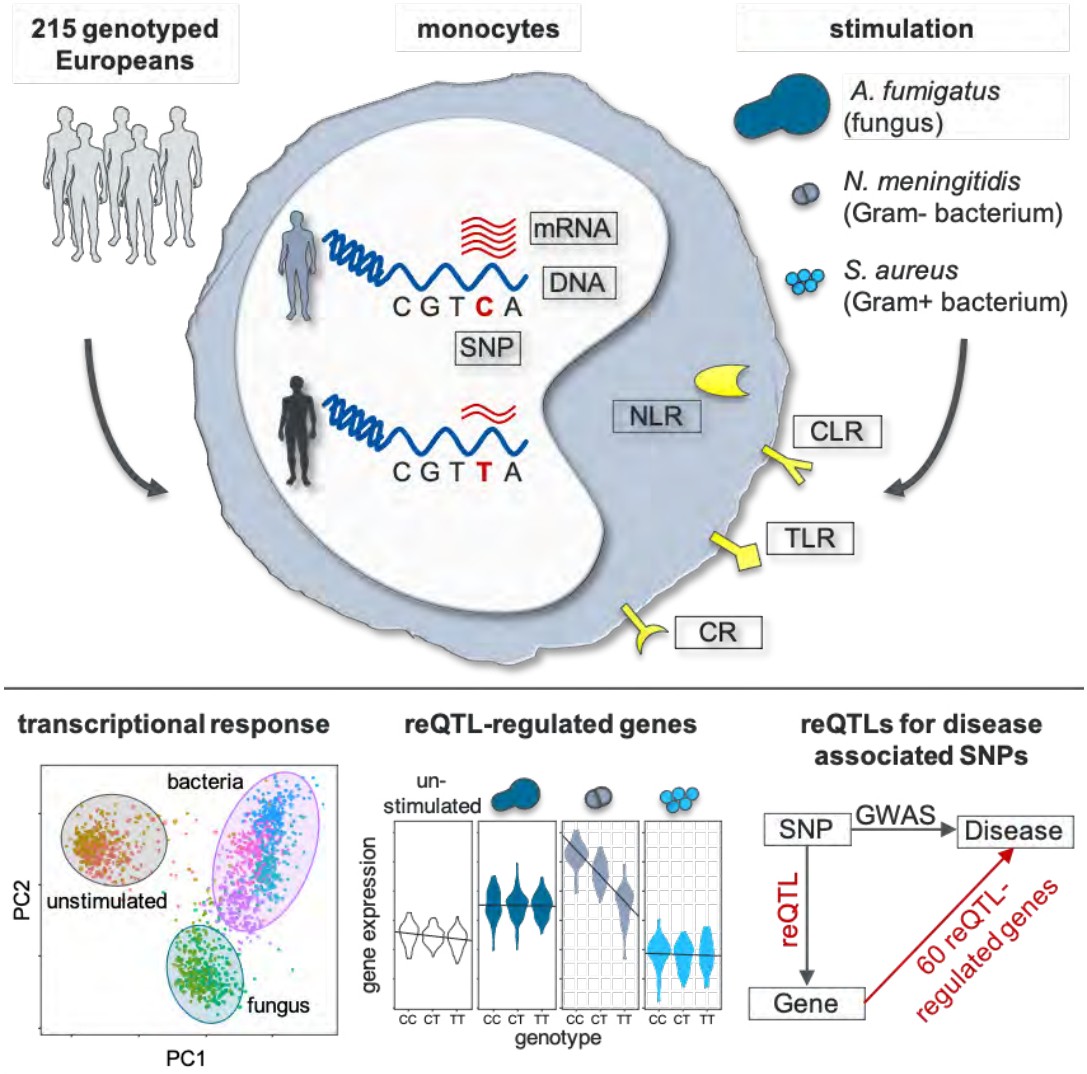

Figure: Innate immune responses vary by pathogen and host genetics. Transcriptomes from monocytes from >200 individuals after stimulation with fungal, Gram-negative or Gram-positive bacterial pathogens were generated. Monocytes showed a conserved response to bacterial pathogens and a distinct antifungal response. Mapping expression quantitative trait loci (eQTLs) identified 745 response eQTLs (reQTLs) and corresponding genes showing pathogen-specific effects. Compared to all differentially expressed genes, reQTL-regulated genes were more frequently upregulated, indicating cell-activating gene regulation. ReQTLs functionally characterize risk variants identified through genome-wide association studies for autoimmunity, inflammatory or infectious diseases and cancer. Thus, in addition to the transcriptional response of monocytes, their genetic regulation differs for bacterial and fungal pathogens.

model to study immune responses towards fungal pathogens and improved automated image analysis algorithms to study host-pathogen interaction (*Sci Rep* 2019). The immune response against pathogens is modulated by genetic variations. To address the impact of genetic variation on immune response patterns we analyzed single nucleotide polymorphisms (SNPs) that contribute to variation in gene expression (expression quantitative trait loci (eQTL)) during infection of monocytes from >200 genotyped donors with fungal and bacterial pathogens. We aim to characterise genetic variants that are associated with IFI and establish models for the functional implications of these genetic variations in cooperation with several European groups. These cooperations have led to the successful application within the host directed medicine call in Horizon 2020 (HDM-Fun, coordinator: F. v.d. Veerdonk, Nijmegen). Finally, new immunomodulatory drugs can also impair antifungal immunity, as shown for Etanercept, a TNF-alpha anatagonist (*Sci Rep* 2019).

Epidemiology, antifungal drug resistance and diagnosis of invasive fungal infections

The NRZMyk is the central point of contact in Germany for all questions related to diagnosis and clinical management of IFI (*Dt Ärzteblatt Int* 2019). The number of samples processed at the NRZMyk has increased continuously (currently >700 / year). Major NRZMyk activities include: (i) Identification of rare fungal pathogens and efforts to improve taxonomic classification. In a DFG-funded project we completely revised the taxonomy of the genus Mucor (*Persoonia* 2020; *Mycopathologia* 2019). (ii) A broad range of available molecular tests for detection of fungal pathogens and (iii) reference susceptibility testing and molecular analysis of resistance (*Nature Comm* 2018; *Antimicrob Agents Chemother* 2019). Within InfectControl, the NRZMyk coordinates a large project on environmental emergence of antifungal drug resistance (FINAR, *mBio* 2020).

The NRZMyk participates in national and international standardisation committees like the Antifungal Susceptibility Testing Subcommittee of EUCAST and the National Antibiotic-Susceptibility Testing Committee (NAK), as well as clinical and epidemiological studies of IFI and development of guidelines and web tools (*Trials* 2018; *Mycoses* 2018). Together with the Department of Ophthalmology at the University Hospital in Düsseldorf, we established and maintain a National Registry for Fungal Keratitis (www.pilz-keratitis.de). Currently we analyse *Fusarium* isolates from keratitis cases to link different infection routes to distinct *Fusarium* sp. One of the major recent challenges was monitoring the national epidemiology of the emerging yeast pathogen *Candida auris*. The NRZMyk has published several statements and recommendations for diagnostic labs and contributed to European initiatives (*Euro Surveill* 2018, 2019). We coordinated analysis of the first cases in Germany and contributed to a global whole genome sequencing project on *C. auris* coordinated by the CDC and

Broad Institute (*Emerg Infect Dis* 2019, *mBio* 2020).

In the next years, we will further shift towards clinically applied research efforts, thus making use of our role as National Reference Center. By providing a link between basic research and clinical application we aim to fulfill a unique and important function within the Leibniz-HKI.

Selected collaborations

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Selected publications

1. Barber AE, Riedel J, Sae-Ong T, Kang K, Brabetz W, Panagiotou G, Deising HB, Kurzai O (2020) Effects of agricultural fungicide use on *Aspergillus fumigatus* abundance, antifungal susceptibility, and population structure. *mBio* 11(6), e02213-20.

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4. Ruben S, Garbe E, Mogavero S, Albrecht-Eckardt D, Hellwig D, Häder A, Krüger T, Gerth K, Jacobsen ID, Elshafee O, Brunke S, Hünniger K, Kniemeyer O, Brakhage AA, Morschhäuser J, Hube B, Vylkova S, Kurzai O, Martin R (2020) Ahr1 and Tup1 contribute to the transcriptional control of virulence-associated genes in *Candida albicans*. *mBio* 11(2), e00206-20.

5. Wagner L, Stielow JB, de Hoog GS, Bensch K, Schwartze VU, Voigt K, Alastruey-Izquierdo A, Kurzai O, Walther G (2019) A new species concept for the clinically relevant *Mucor circinelloides* complex. *Persoonia* 42, 67-97.

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

Research Group

MICROBIAL IMMUNOLOGY

MICROBIAL IMMUNOLOGY

Mission

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.

Most important results

The Research Group Microbial Immunology focuses on *C. albicans* as both a commensal and a pathogen. Both, as a commensal and pathogen, *Candida* interacts not only with the host but also with members of the bacterial microbiota. Thus, one focus of our research are interactions between *C. albicans* and bacteria. Another main topic is the pathogenesis of infections and the role of the host response in pathogenesis.

Only few distinct bacterial species responsible for colonisation resistance have yet been identified. In a project that is part of the CRC/TR FungiNet, we aim to identify additional bacteria conferring colonization resistance by utilising natural microbiome variation in laboratory mice. Following microbiome analysis by 16S and ITS sequencing of faecal samples, five out of 15 analysed C57Bl/6 breeding colonies were selected based on microbiome differences for colonization experiments. While we could confirm that antibiotic-induced dysbiosis enhances colonization with *C. albicans*, we made the surprising discovery that in several mouse breeding cohorts stable colonisation occurs in the absence of antibiotic treatment. This is in contrast to several previous reports that adult laboratory mice are naturally resistant to *C. albicans* colonization, and will be followed up to identify the mechanisms underlying differences in colonization resistance. In collaboration with the group of Christian Kosan (FSU Jena), we furthermore observed variations in the immune cell populations of peripheral and central lymphatic organs between the mouse cohorts prior to treatment and after *Candida* colonization. As the mice have the same genetic background this is likely due to differences in microbiota composition.

Another level of fungal-bacterial interactions are coinfections, which apply to approx. 30% of disseminated candidiasis cases. One of the most common *Candida*-associated bacteria identified during mixed infections are enterococci, of which *E. faecalis* accounts for most incidences. In mice, *C. albicans* and *E. faecalis* form a microbial community that dominates the microbiota following antibacterial treatment. Using *in vitro* models developed in collaboration with the Leibniz-HKI department MPM and the group of A. Mosig from the UKJ (*Biomaterials* 2019; *mBio* 2018), we found that the quality *of E. faecalis-C. albicans* coinfection of enterocytes is highly strain-dependent, ranging from antagonistic to synergistic. Using selected strains, these strain-dependent types of interaction were confirmed *in vivo* in mice in collaboration with Marc Swidergall (UCLA). Although *Candida* hyphae promoted host cell invasion by enterococci, the synergistic damage was independent of fungal filamentation, other fungal virulence factors, physical contact of fungi to either host cells or bacteria, and was also promoted by non-pathogenic fungal species such as *Saccharomyces cerevisiae*. In contrast, synergistic damage correlated with the hemolytic activity of *E. faecalis*, and can be transferred by conjugative plasmids, suggesting that the *E. faecalis* hemolysin is responsible for enhanced damage. Enhanced bacterial host cell damage can also be induced by *C. albicans*-conditioned media and we identified glucose depletion by the fungus as one factor that enhances host cell damage by *E. faecalis*. Furthermore, we observed synergistic host damage

depending on a bacterial haemolysin also for *Candida* and *Proteus mirabilis* interactions, which is mediated by a glucose-independent mechanism. Together, this suggests a more general impact of bacterial-fungal interactions on bacterial virulence with consequences for host cell damage and pathogenesis.

Systemic candidiasis requires dissemination via the blood stream. To investigate this crucial step, we developed murine and avian whole blood models in collaboration with Fungal Septomics (O. Kurzai) which were analyzed with the help of the research group ASB (T. Figge) as part of the Leibniz ScienceCampus InfectoOptics. In this recently completed project, we demonstrate differences in host-pathogen interactions depending on the pathogen, host species, and also host genetics (*Front Immunol* 2020 and 2021). Most important are the differences we observed between murine and human blood as this has implications for the transferability of results obtained in murine models to human patients. Nonetheless, mouse models remain the gold standard for studying fungal infections *in vivo*, and our specific expertise in animal models has led to several collaborations resulting in over 10 publications in the last three years. This includes a publication together with F. Rosenbauer (Münster) (*Nat Immunol* 2019), in which we investigate the role of the myeloid transcription factor PU.1 for neutrophil function during candidiasis. We found that as well as providing the transcriptional prerequisite for eradicating pathogens, the predom-

Figure: *Enterococcus faecalis* (purple) adhering to *Candida albicans* hyphae (green).

inant function of PU.1 was to restrain the neutrophil defense by broadly inhibiting the accessibility of enhancers via the recruitment of histone deacetylase 1. Such epigenetic modifications impeded the immunostimulatory AP-1 transcription factor JUNB from entering chromatin and activating its targets. This highlights the essential function of neutrophils for the host defense in systemic candidiasis but also the necessity to regulate neutrophil recruitment and function to prevent and excessive and detrimental innate immune response.

In the next years, we will continue our research on pathogenesis of systemic candidiasis by further analyzing host and fungal factors contributing to disease development. Another focus to be continued are fungal-bacterial interactions, by further elucidating the role of metabolic-cross talk between fungi and bacteria and other microbial factors for virulence and pathogenesis. This will include metabolomic analyses of *Candida-Enterococcus* interactions in collaboration with S. Vylkova (HFI) and an international collaboration with S. Coulthurst (Dundee), funded by the Wellcome Trust. With S. Coulthurst we will assess the relevance of the bacterial potential to damage fungal cells *via* injection of antifungal effector proteins. Furthermore, given the mounting evidence of microbiome-mediated effects on host immunity, we have recently started a project addressing the role of the microbiome in general, and *C. albicans* colonization specifically, for the host response to systemic candidiasis. This project is funded as part of the ITN FunHoMic and the Cluster of Excellence Balance of the Microverse.

Selected collaborations

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Selected publications

1. Fischer J, Walter C, Tönges A, Aleth H, Jordão MJC, Leddin M, Gröning V, Erdmann T, Lenz G, Roth J, Vogl T, Prinz M, Dugas M, Jacobsen ID, Rosenbauer F (2019) Safeguard function of PU.1 shapes the inflammatory epigenome of neutrophils. *Nat Immunol* 20, 546-558.

2. Halder LD, Jo EAH, Hasan MZ, Ferreira-Gomes M, Krüger T, Westermann M, Palme DI, Rambach G, Beyersdorf N, Speth C, Jacobsen ID, Kniemeyer O, Jungnickel B, Zipfel PF, Skerka C (2020) Immune modulation by complement receptor 3-dependent human monocyte TGF-ß1-transporting vesicles. *Nat Commun* 11, 2331.

3. Machata S, Müller MM, Lehmann R, Sieber P, Panagiotou G, Carvalho A, Cunha C, Lagrou K, Maertens J, Slevogt H, Jacobsen ID (2020) Proteome analysis of bronchoalveolar lavage fluids reveals host and fungal proteins highly expressed during invasive pulmonary aspergillosis in mice and humans. *Virulence* 11, 1337-1351.

4. Maurer M, Gresnigt MS, Last A, Wollny T, Berlinghof F, Pospich R, Cseresnyes Z, Medyukhina A, Graf K, Gröger M, Raasch M, Siwczak F, Nietzsche S, Jacobsen ID, Figge MT, Hube B, Huber O, Mosig AS (2019) A three-dimensional immunocompetent intestine-on-chip model as *in vitro* platform for functional and microbial interaction studies. *Biomaterials* 220, 119396.

5. Sreekantapuram S*, Lehnert T*, Prauße MT, Berndt A, Berens C, Figge MT**, Jacobsen ID** (2020) Dynamic interplay of host and pathogens in an avian whole blood model. *Front Immunol* 11, 500. *authors contributed equally; **corresponding authors

Major third party funding

DFG: Cluster of Excellence Balance of the Microverse

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

EU: Marie-Skłodowska-Curie Innovative Training Network FunHoMic – Deciphering the fungus-host-microbiota interplay to improve the management of fungal infections

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

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Healthy-enriched species

Research Group

SYSTEMS BIOLOGY AND BIOINFORMATICS

SYSTEMS BIOLOGY AND BIOINFORMATICS

Mission

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 data, and ending with experimental validation.

Most important results

Our research is highly collaborative and explores the role of the microbiome in globally significant diseases for delivering novel patient-centric therapies. We are studying several diseases that fall under the following broad categories: infection (local collaborators include Axel Brakhage, Bernhard Hube, Oliver Kurzai, Ilse Jacobssen, Hortense Slevogt, among many others), critical care (local collaborators include Michael Bauer, Thomas Kamradt, both UKJ), cancer (international collaborators) and metabolic diseases (international collaborators). We are also particularly interested in the dynamics between host and the associated microbes (local collaborators include Ian Baldwin, Matthew Agler, Georg Matziolis, Christine Beemelmanns among many others). We also develop drug-disease interaction networks to assess reversal of the sepsis biological signature in subgroups of patients. By establishing multidimensional molecular networks that provide insights into sepsis network responses to drug perturbations, we aim to improve our ability to design new therapies and predict patient groups who are likely to respond to specific treatments.

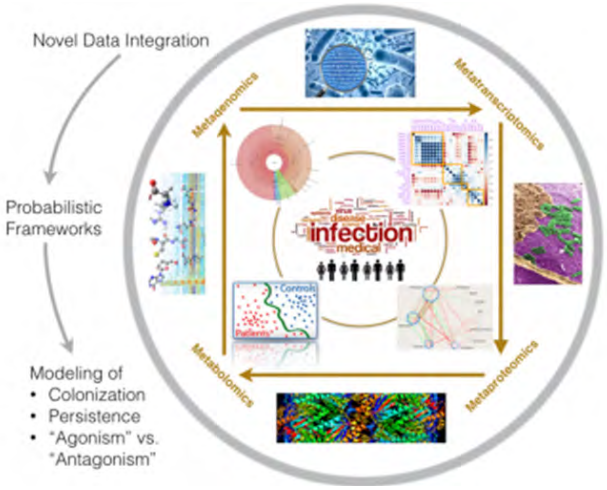

Figure: Develop models that describe the interplay of hosts, commensal microbes and diseases.

The group is currently coordinating the Horizon 2020 ITN BestTreat (16 international partners) and it is a member of the Cluster of Excellence Balance of the Microverse, Area of Excellence Hong Kong Institute of Metabolic Diseases and CRC/TR FungiNet and Collaborative Research Fund MarineGEO Hong Kong.

The group is publishing in the last three years in top journals in the field (*Cell Reports*, *GigaScience*, *Cell Metabolism*, *Microbiome* (often)) and the head of the group holds the corresponding author position in the majority (if not all) of them.

Perspective

Our research is highly collaborative and explores the role of the microbiome and mycobiome in globally significant diseases for delivering novel patient-centric therapies. We are particularly interested on the dynamics between the host and the associated bacteria and fungi in metabolic diseases, infection, critical care and cancer. SBI is emphasizing on the integration of microbiome, mycobiome and meta-omics data with biochemical and clinical data for in-depth investigation of the biotic and abiotic factors consistently associated with alterations in host's metabolism and physiology. We construct state-of-the-art genome-scale metabolic models for fungal pathogens, and we use *in silico* growth simulations to understand the interactions between the host, the resident microbiota and the pathogen. Our data provide

'real world' understanding of microbiome and mycobiome functions valuable for precision medicine and targeted microbial therapies.

In parallel, we generate an enormous volume of next generation sequencing data and we develop computational pipelines for efficient and informative data processing. We perform comparative genomics and transcriptomics of fungal pathogens to explore how genetic variation contributes to human infection and antifungal drug resistance. We apply machine learning methods that combine clinical and high-throughput biological data to study sepsis and we establish multidimensional molecular networks to improve our ability to design new therapies and predict patient groups who are likely to respond to specific treatments.

The research focus of SBI is

- to identify signatures of microbiome dysbalance that allow for early detection of disease,
- to shape and control microbial consortia to create beneficial impact in patients with chronic diseases,
- to understand the interactions between bacteria and fungi and how these interactions can prevent systemic infections from opportunistic fugal pathogens.

Selected collaborations

Baker, David
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Sommer, Morten
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Xu, Aimin
The University of Hong Kong, China

Selected publications

1. Heshiki Y, Vazquez-Uribe R, Li J, Ni Y, Quainoo S, Imamovic L, Li J, Sørensen M, Chow BKC, Weiss GJ, Xu A, Sommer MOA, Panagiotou G (2020) Predictable modulation of cancer treatment outcomes by the gut microbiota. *Microbiome* 8, 28.

2. Liu Y*, Wang Y*, Ni Y*, Lam KSL, Wang Y, Xia Z, Tse MA**, Panagiotou G**, Xu A** (2020) Gut microbiome fermentation determines the therapeutic efficacy of exercise on insulin resistance in individuals with prediabetes. *Cell Metab* 31, 77-91.e5. *equal contribution, ** corresponding authors

3. Mirhakkak M*, Schäuble S*, Klassert T, Brunke S, Brandt P, Loos D, Uribe R, de Oliveira Lino FS, Ni Y, Vylkova S, Slevogt H, Hube B, Weiss G, Sommer M, Panagiotou G (2020) Metabolic modeling predicts specific gut bacteria as key determinants for *Candida albicans* colonization levels. *ISME J* 15, 1257-1270. *equal contribution

4. Seelbinder B, Chen J, Brunke S, Uribe RV, Meyer AC, de Oliveira Lino FS, Chan KF, Loos D, Imamovic L, Tsang CC, Lam RPK, Sridhar S, Kang K, Hube B, Woo PCY, Sommer MOA, Panagiotou G (2020) Antibiotics create a shift from mutualism to competition in human gut communities with a longer-lasting impact on fungi than bacteria. *Microbiome* 8, 133.

5. Seelbinder B, Wallstabe J, Marischen L, Weiss E, Wurster S, Page L, Loffler C, Bussemer L, Schmitt AN, Wolf T, Linde J, Cicin-Sain L, Becker J, Kalinke U, Vogel J, Panagiotou G, Einsele H, Westermann AJ, Schauble S, Loeflller J (2020) Triple RNA-seq reveals synergy in a human virus-fungus co-infection model. *Cell Reports* 33, 108389.

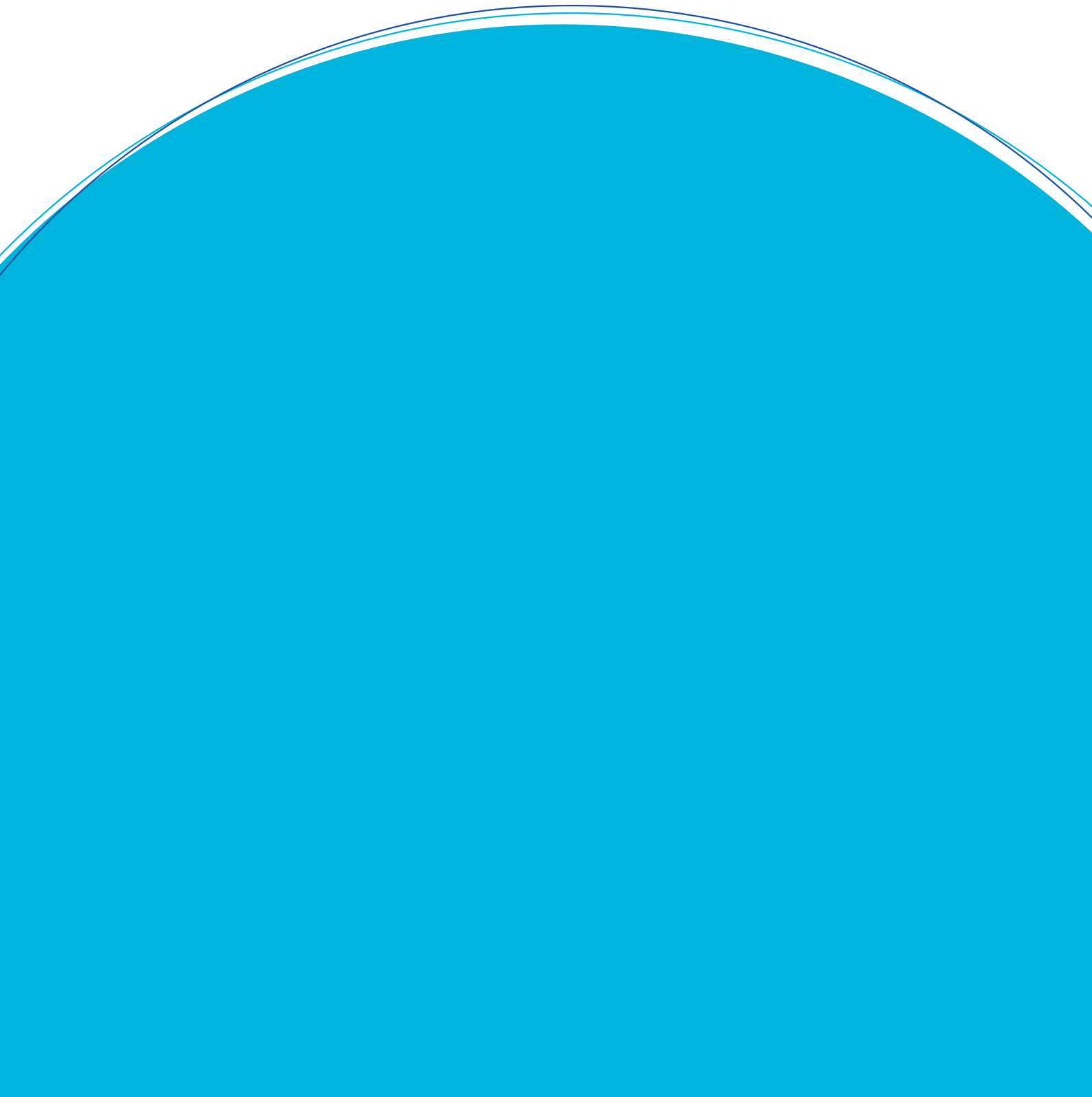
Major third party funding

EU: ITN BestTreat - Building a Gut Microbiome Engineering Toolbox for In-Situ Therapeutic Treatments for Non-alcoholic Fatty Liver Disease

DFG: Cluster of Excellence Balance of the Microverse – Junior Research Group Fungal Informatics

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



LEIBNIZ-HKI

Independent
Junior Research Group

ADAPTIVE PATHOGENICITY STRATEGIES

ADAPTIVE PATHOGENICITY STRATEGIES

Mission

We investigate the adaptations to infections with *Candida albicans* induced by host conditions (like temperature) and host molecules. In particular, we are interested in the underlying molecular mechanisms inducing these adaptations and the host proteins the fungus may sense to do so.

Most important results

In May 2020, the German Research Foundation (DFG) granted funding for a Research group within the Emmy Noether program to Mark Gresnigt (Department of Microbial Pathogenicity Mechanisms (MPM)). This funding led to the establishment of a new Junior Research Group at the Leibniz-HKI named Adaptive Pathogenicity Strategies (APS) headed by M. Gresnigt. This independent research group shares laboratory space with the MPM.

The APS focusses on three research topics: fungal adaptation to the host (DFG, Humboldt Foundation, ESCMID), the influence of immunotherapy on host-pathogen interactions (HDM-Fun with MPM), and the influence of the microbiota on fungal pathogenicity (Microverse with MPM, FunHoMic with MPM). The APS team has used cell-culture, microbiological, and biochemical methods to study the interaction between *C. albicans* and host serum proteins and immune mediators (topic: fungal adaptation to the host). We have discovered that the abundant serum protein albumin modulates *C. albicans* pathogenicity by interacting with the toxin candidalysin (MSc thesis S. Austermeier). In collaboration with the team of J. Naglik in London, we demonstrated that candidalysin is unable to cause damage in host niches that contain high levels of albumin (manuscript in preparation). In contrast, the serum protein and immune mediator α1-antitrypsin fostered *C. albicans* pathogenicity by increasing filamentous growth (BSc thesis P. Porschitz). In collaboration with the MPM, we have begun to explore the influence of immunotherapy on host-pathogen interactions. Interferon(IFN)γ is being experimentally explored as immunotherapy for candidiasis (HDM-Fun), yet apart from that it augments macrophage fungicidal capacity, little is known about the mechanisms and its effect on host-pathogen interactions. When including IFNγ in a *C. albicans* translocation model, we made the observation that it facilitates higher fungal translocation rates. These data were subsequently used to design a project for the third funding period of FungiNet (see above) that investigates the impact of immunotherapy on fungal translocation and pathogenicity mechanisms. We have previously demonstrated the potential of *Lactobacillus rhamnosus* to antagonize *C. albicans* pathogenicity. In 2020 we have continued to explore the molecular and metabolic interactions of this antagonistic potential. We also established in vitro models to study fungal host-microbiota interactions relevant for vulvovaginal candidiasis, including a VVC-on-chip model. Since all supervised doctoral researchers have only recently started their projects, these data are not yet published.

Selected collaborations

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LeibunGut-Landmann, Salome
University of Zurich, Switzerland

Netea, Mihai
Radboud University, Nijmegen, Netherlands

van de Veerdonk, Frank
Radboud University, Nijmegen, Netherlands

Selected publications

1. Austermeier S, Kasper L, Westman J, Gresnigt MS (2020) I want to break free - macrophage strategies to recognize and kill *Candida albicans*, and fungal counter-strategies to escape. *Curr Opin Microbiol* 58, 15-23.

2. d'Enfert C, Kaune AK, Alaban LR, Chakraborty S, Cole N, Delavy M, Kosmala D, Marsaux B, Fróis-Martins R, Morelli M, Rosati D, Valentine M, Xie Z, Emritloll Y, Warn PA, Bequet F, Bougnoux ME, Bornes S, Gresnigt MS, Hube B, Jacobsen ID, Legrand M, Leibundgut-Landmann S, Manichanh C, Munro CA, Netea MG, Queiroz K, Roget K, Thomas V, Thoral C, Van den Abbeele P, Walker AW, Brown AJP (2020) The impact of the Fungus-Host-Microbiota interplay upon *Candida albicans* infections: current knowledge and new perspectives. *FEMS Microbiol Rev* , fuaa060.

3. de Graaf DM, Maas RJA, Smeekens SP, Eisenmesser E, Redzic JS, Helsen MM, Powers NE, Li S, Kalabokis V, Gresnigt MS, Joosten LAB, Dinarello CA, van de Veerdonk FL (2020) Human recombinant interleukin-38 suppresses inflammation in mouse models of local and systemic disease. *Cytokine* 137, 155334.

4. Kumamoto CA, Gresnigt MS, Hube B (2020) The gut, the bad and the harmless: *Candida Albicans* as a commensal and opportunistic pathogen in the intestine. *Curr Opin Microbiol* 56, 7-15.

Major third party funding

DFG: Emmy Noether Junior Research Group

Independent
Junior Research Group

BIOBRICKS OF MICROBIAL NATURAL PRODUCT SYNTHESES

BIOBRICKS OF MICROBIAL NATURAL PRODUCT SYNTHESES

Mission

The mission of the BMN group 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.

Most important results

The work of the BMN group is focused on the study of eukaryotic secondary metabolites (SMs) with a special interest on compounds having industrial and therapeutic applications. We are developing new methods for the production of active compounds *in vitro* and *in vivo*, with special emphasis on precursors, e.g. CoA esters, and key biosynthetic enzymes. The competitiveness of the group is enhanced by hosting different fields of expertise specialized in synthetic biology, biochemistry, and chemical biology. This makes the BMN group one of the few groups in Germany employing synthetic biology to study eukaryotic SMs.

1. Regulation of SMs in fungi.

Overall understanding of SM biosynthesis has increased significantly in the past few decades. However, little is known about the regulation and cellular compartmentalization of SM biosynthetic pathways in fungi. DHN-melanin is one of the most studied SM playing an important role in *Aspergillus fumigatus* virulence. DHN-melanin is transported to the cell-wall through cellular compartments named melanosomes. In cooperation with the University of São Paulo (Brazil) and the Department Molecular and Applied Microbiology at the Leibniz-HKI, we have elucidated the pheromone signalling pathway in *A. fumigatus* proving its involvement in the regulation of DHN-melanin (*mBio* 2019). Apart from melanin, other pathways are embedded in organelles, raising the question how fungal cells create and maintain compartments that host SM biosynthesis. We have started to answer this question by studying the biosynthesis of sphingolipid inhibitors (SIs) in fungi. This extraordinary class of molecules, which act primarily as mycotoxins, can potentially be used to disclose mechanisms beyond the compartmentalization of metabolites. Fumonisin FB_1 from *Fusarium verticillioides* is a potent toxin targeting the core sphingolipid biosynthetic enzyme ceramide synthase (CS). Localization studies revealed aminotransferase Fum8 is localized in intracellular vesicles derived from the endoplasmic reticulum, hosting as well the sphingolipid biosynthetic enzymes. Phylogenetic analysis indicated that the hitherto uncharacterized Fum18 is a CS homolog. The ability of *FUM18* to fully complement the yeast CS null mutant, demonstrated that it is a functional CS. Cell viability assays revealed that Fum18 contributes to the fungal self-protection against FB_1 and increases resistance by providing FUM cluster-encoded CS activity (*mBio* 2020).

With the support of the European Social Fund and the Free State of Thuringia we started a project, SphinX, aimed to investigate the SIs chemical variability and compartmentalization in fungi. Analysis of genome databases revealed that there are more than 300 potential SI gene clusters. We identified the cluster responsible for the biosynthesis of sphingofungins in *A. fumigatus*. In addition, analysis of tagged fluorescent biosynthetic enzymes revealed that sphingofungin biosynthesis also occurs in specialized compartments.

2. Heterologous expression of biosynthetic gene clusters.

The heterologous expression of biosynthetic gene clusters can be a feasible solution to decrypt unknown fungal SMs. By exploiting the "stop-carry on" mechanism of picornaviruses, we have designed an easy-to-assemble vector system to heterologously express multiple genes under the control of a single promoter. In cooperation with the Department Pharmaceutical Microbiology at the Friedrich Schiller University this method was successfully applied to produce the psychotropic mushroom alkaloid psilocybin in high yields by heterologous expression of the entire biosynthetic gene cluster from *Psilocybe cubensis* in the mould *Aspergillus nidulans* (*Metab Eng* 2018).

3. Rational design of synthetic metabolic pathways

Cell-free production pathways are becoming a very attractive alternative for the production of market-relevant molecules. *In vitro* multicatalytic reactions offer the opportunity to use recombinant enzymes from different sources, leading to the biosynthesis of new non-natural derivatives. In order to produce precious chemical precursors, enzymes responsible for the synthesis of different CoA-activated esters were isolated and purified and subsequently immobilized on synthetic surfaces, ensuring the recycling of expensive cofactors during catalysis. (*ACS Appl Mater Interfaces* 2020).

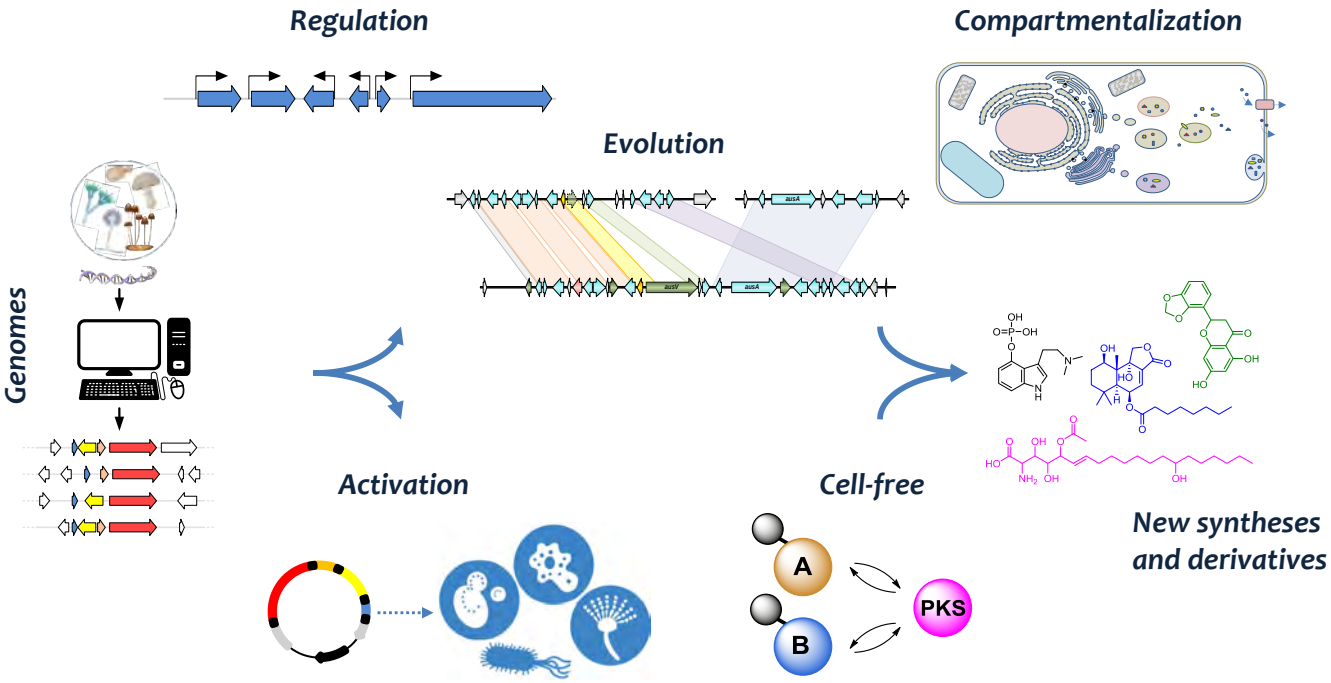

Figure: Strategy for discovering and producings new active compounds.

The same approach was established to produce plant-derived active molecules. In particular, we focused our attention on aromatic polyketides, such as flavonoids and stilbenoids, which are natural polyphenolic compounds having a broad spectrum of activities. They are mainly produced by type III polyketide synthases (PKSs), homodimeric proteins that synthesize long carbon chain molecules in an iterative fashion. Despite their eukaryotic origin, many type III PKSs and CoA ligases are actively produced when expressed in *E. coli*. Moreover, since most enzymes are flexible in terms of substrate scope, the chemical variability of aromatic polyketides can be increased by varying the used building blocks.

We expressed and purified malonyl-, coumaroyl-, and benzoyl-CoA ligases from plants and bacteria that have been combined with stilbene and chalcone synthases. Thanks to this methodology we could easily investigate the substrate promiscuity of all enzymes in parallel. Additionally, this knowledge was used to synthetically modify coumaric acid derivatives that yielded novel unnatural aromatic polyketides (*ACS Synth Biol* 2020).

Selected collaborations

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

Freier, Erik
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Goldman, Gustavo
Universidade de São Paulo, Brasil

Haas, Hubertus
Medical University Innsbruck, Austria

Hoffmeister, Dirk
Friedrich Schiller University, Jena, Germany

Proctor, Robert H.
United States Department of Agriculture, Peoria, USA

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

Selected publications

1. Hoefgen S, Lin J, Fricke J, Stroe MC, Mattern DJ, Kufs JE, Hortschansky P, Brakhage AA, Hoffmeister D, Valiante V (2018) Facile assembly and fluorescence-based screening method for heterologous expression of biosynthetic pathways in fungi. *Metab Eng* 48, 44-51.

2. Janevska S, Ferling I, Jojić K, Rautschek J, Hoefgen S, Proctor RH, Hillmann F, Valiante V (2020) Self-protection against the sphingolipid biosynthesis inhibitor fumonisin B1 is conferred by a FUM cluster-encoded ceramide synthase. *mBio* 11, e00455-20.

3. Krishnan BP, Prieto Lopez LO, Hoefgen S, Xue L, Wang S, Valiante V, Cui J (2020) A thermo-magneto-responsive smart biocatalyst for malonyl Coenzyme A synthesis. *ACS Appl Mater Interfaces*, 12(18), 20982-20990.

4. Kufs JE, Hoefgen S, Rautschek J, Bissell AU, Graf C, Fiedler J, Braga D, Regestein L, Rosenbaum MA, Thiele J, Valiante V (2020) Rational design of flavonoid production routes using combinatorial and precursor-directed biosynthesis. *ACS Synth Biol* 9(7), 1823-1832.

5. Manfiolli AO, Siqueira FS, Dos Reis TF, Van Dijck P, Schrevens S, Hoefgen S, Föge M, Straßburger M, de Assis LJ, Heinekamp T, Rocha MC, Janevska S, Brakhage AA, Malavazi I, Goldman GH, Valiante V (2019) Mitogen-Activated Protein Kinase Cross-Talk Interaction Modulates the Production of Melanins in Aspergillus fumigatus. *mBio* 10, pii: e00215-19.

Major third party funding

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

Free State of Thuringia: Researcher Group SphinX - Sphingolipid-Inhibitoren – ein neues therapeutisches Konzept

LEIBNIZ-HKI

Independent
Junior Research Group

BIOSYNTHETIC DESIGN OF NATURAL PRODUCTS

BIOSYNTHETIC DESIGN OF NATURAL PRODUCTS

Mission

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.

Most important results

The Independent Junior Research Group Biosynthetic Design of Natural Products (BDN) aims to redesign biosynthetic pathways of natural products for the development of novel bioactive molecules with a focus on nonribosomal peptide synthetases (NRPS) and antibiotics. In the design process, we are using tools from enzymology, synthetic biology and enzyme engineering. Our vision is to routinely tailor bioactive natural products for drug development through biosynthetic engineering. Biotechnological methods for generating new drugs would be environmentally more sustainable than total chemical synthesis currently applied in medicinal chemistry. Hence, we address two major challenges with our work – the shortage of antibiotics and the need for green, biocatalytic methods in industry.

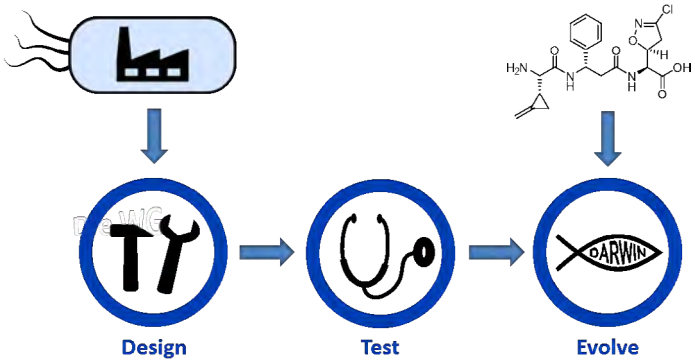

Figure: When efficient pipelines for engineering, diagnosing, and repairing nonribosomal peptide synthetases can be developed, creativity knows no limits for the diversity of peptides that could be biosynthesized.

DNA-templated NRPS: We have engineered DNA-templated NRPSs (DT-NRPSs) which we propose as a new tool for biocatalytic peptide synthesis. In NRPS, each module selects and incorporates one amino acid into a peptide and the sequence of modules, usually fixed by a covalent link between them, determines the product outcome. Hsin-Mei Huang has achieved high levels of activity with engineered NRPS modules assembled on DNA via DNA-binding zinc finger domains (*Cell Chem Biol* 2021). We studied the geometric requirements for productive assembly by varying the distance between module binding sites on the DNA and found astonishing flexibility. Remarkably, also module-skipping or repetition could be programmed by adding different DNA templates, leading to non-natural peptide sequences. DT-NRPSs showcase a fundamentally new concept for biocatalysis where unprotected building blocks are polymerized in a programmable fashion.

Specificity profiling of NRPSs: NRPS engineering and discovery require specificity profiling of modules (*ChemBioChem* 2019). Aleksa Stanišić has developed a novel assay format that allows multiplexed and highly sensitive measurements of nonribosomal substrate activation (*Chem Sci* 2019). With the hydroxamate assay (HAMA), we have recorded the entire specificity profile of the NRPS modules in a single measurement, which would have previously taken weeks to do. We have used the novel assay as a tool for NRPS discovery and for screening mutant libraries for altered specificities in a directed evolution experiment. Proof-of-principle for the utility of HAMA in natural product discovery has been established by tentatively elucidating the specificity of an unusual, cryptic NRPS from microalgae in collaboration with Severin Sasso (Uni Leipzig). Further collaborations based on HAMA and the characterization of A-domains have been initiated with the labs of Christian

Hertweck (HKI; *Angew Chem Int Ed* 2020), Pierre Stallforth (HKI; *Chem Sci* 2019) and Markus Gressler (FSU/HKI; *Appl Env Microbiol* 2020).

Supercharged peptides: In order to tune antibiotic properties of peptides for medical applications, it is often desirable to modify their charge state because bacterial membranes tend to be more negatively charged than human ones. Philipp Stephan (ILRS) is exploring methods for replacing uncharged proline residues with positively charged ornithine to make the model antibiotic gramicidin S less toxic. Instead of incorporating the ornithine directly, we use an uncharged amino acid similar to proline (piperazic acid) which can be reductively converted into ornithine post-biosynthetically. Incorporation of piperazic acid is facilitated by the structural similarity to proline but nevertheless proceeds inefficiently with the wild-type NRPS. We have enhanced piperazic acid incorporation by directed evolution, resulting in a ca. 60-fold higher incorporation. We seek to develop this strategy to produce enhanced gramicidin S.

Evolving antibiotic production in microfluidics: In collaboration with Miriam Agler-Rosenbaum (Leibniz-HKI), we have developed a microfluidic assay for gramicidin S production. Farzaneh Pourmasoumi (JSMC/DAAD) has detected the antibiotic activity of gramicidin S producing *E. coli* in microfluidic droplets through lysis or fluorogenic reporter liposomes. This assay will be further validated and employed for directed evolution experiments on the gramicidin S cluster.

Outlook: DT-NRPS is a highly innovative concept for synthetic biology which should be improved and expanded in several directions in the next years to become the major focus of our work. The DT-NRPS concept will be optimized for synthetic applications and potential commercialization by tuning reaction conditions, and testing enzyme immobilization and alternative DNA-binding methods and expanding the method to polyketides.

Selected collaborations

Freier, Erik
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Selected publications

1. Götze S, Arp J, Lackner G, Zhang S, Kries H, Klapper M, García-Altares M, Willing K, Günther M, Stallforth P (2019) Structure Elucidation of the Syringafactin Lipopeptides Provides Insight in the Evolution of Nonribosomal Peptide Synthetases. *Chem Sci* 10, 10979-10990.

2. Huang HM, Stephan P, Kries H (2020) Engineering DNA-templated nonribosomal peptide synthesis. *Cell Chem Biol* 28, 221.-227.e7.

3. Stanisic A, Hüsken A, Kries, H (2019) HAMA: A multiplexed LC-MS/MS assay for specificity profiling of adeynlate-forming enzymes. *Chem Sci* 10, 10395-10399.

4. Trottmann F, Ishida K, Franke J, Stanišić A, Ishida-Ito (2020) Sulfonium acids loaded onto an unusual thiotemplate assembly line construct the cyclopropanol warhead of a *Burkholderia* virulence factor. *Angew Chem Int Ed* 59, 13511-13515.

5. Wurlitzer J, Stanišić A, Wasmuth I, Jungmann S, Fischer D, Kries H, Gressler M (2020) Bacterial-like nonribosomal peptide synthetases produce cyclopeptides in the zygomycetous fungus *Mortierella alpina*. *Appl Environ Microbiol*, epub ahead of print.

Major third party funding

DFG: Research Grant Gerichtete Evolution von Adenylierungs-Domänen geleitet von Hydroxamat-Profilen

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

Leibniz Seed money: Enzyme evolution by catalysis enhanced diffusion

LEIBNIZ-HKI

Independent
Junior Research Group

CHEMICAL BIOLOGY OF MICROBE-HOST INTERACTIONS

CHEMICAL BIOLOGY OF MICROBE-HOST INTERACTIONS

Mission

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, including the fungus-growing termite system and the colonial hydroid polyp *Hydractinia echinata*.

Most important results

The Junior Research Group *Chemical Biology of Microbe-Host Interactions* headed by Christine Beemelmanns focusses on the isolation and characterization of microbially produced small molecules that play key roles in two complementary symbiotic model systems to understand their functions, structure-activity relations and the underlying biosynthesis.

Chemical Ecology of the fungus-growing termite system: The ancient fungus-growing termite system serves as a model system to study aspects of defensive and nutritional microbial symbiosis with a major focus on the microbial interplay between the fungal mutualist *Termitomyces* the fungal co-evolved parasite *Pseudoxylaria* and co-residing symbiotic bacteria. The work is funded by the DFG within the frame of the collaborative research center ChemBioSys and the excellence clsuter Microverse. In the first subproject (funded by CRC ChemBioSys and DFG), the group described the bacterial diversity present within the termite system using a cultivation and activity-based isolation approach. Phylogenetic and taxonomic analysis of bacterial isolates revealed that termite colonies are browsing hotspot for bacterial species diversification (*IJSEM* 2020a; *IJSEM* 2020b, *IJSEM* 2020c (in collaboration: Leibniz-HKI Bio Pilot Plant). Although single bacterial species have likely multiple yet often undetermined functions within the system, results indicate towards a more general indirect line of defense against invasive species by the simultaneous secretion of a broad diversity of antibiotics (*Antibiotics* 2018, *Sci Rep* 2019, *J Nat Prod* 2020a and 2020b). Genome- and metabolome-driven analysis of selected bacterial symbionts let to the isolation of a plethora of novel natural products with novel chemotypes of pharmacological interest (collaboration with Leibniz-HKI Bio Pilot Plant: *Chemistry* 2018a, 2019b, *Org Lett* 2020). Biosynthetic pathway analysis of two novel group pf compounds (rubterolones and actinospirols) revealed unique combinations of PKS-based transformations and oxidative rearrangements that are responsible for the formation of these chemical scaffolds and future studies are now directed at understanding several of these unprecedented biocatalytic transformations. In a second subproject (CRC ChemBioSys), the group analysed the fungal symbiont *Termitomyces* on a genomic and metabolomic level to study its metabolic properties. Headspace analysis indicated the secretion of a broad diversity of volatiles that have redox-active properties and are known to influence fungal growth and insect feeding behaviour. Genome and transcriptome analysis revealed more than 30 putative terpene cyclases that could be responsible for terpene production. First, heterologous expression of three key enzymes allowed assigning the products to the respective enzymes and mechanistic studies (*Org Bio Chem* 2019). Future studies are directed towards expanding the heterologous expression of key genes of *Termitomyces* to assign identified molecules to proteins and genes. Isolated redox-active metabolites were identified to assist lignin-degrading activity of the mutualistic fungus and future studies are directed towards understanding the synergistic interplay between small molecule and enzymatic-driven wood degrading activity. In frame of the Microverse Excellence cluster project *Termiverse*, the group has

pursued transcriptomic and PacBio sequencing of the mututalist *Termitomyces* and the co-evolved stowaway fungus *Pseudoxylaria* that allowed for a better annotation and in-depth phylogenetic analysis of metabolic traits. Fungus-fungus co-cultivation studies were pursued to identify mechanisms on how the fungus outcompetes the fungal mututalist *Termitomyces* and to support the *in silico* analysis. In frame

In the second model system the group started to investigate the *Pagurus-Hydractinia*-bacteria system (funded by the ERC Starting Grant MORPHEUS from 2019 onwards) to characterize key cross-kingdom signalling molecules and response mechanisms (*J Chem Ecol* 2018). The marine colonial hydroid *Hydractinia* belongs to an early branching metazoan lineage and reproduces through a larval stage, which upon per-

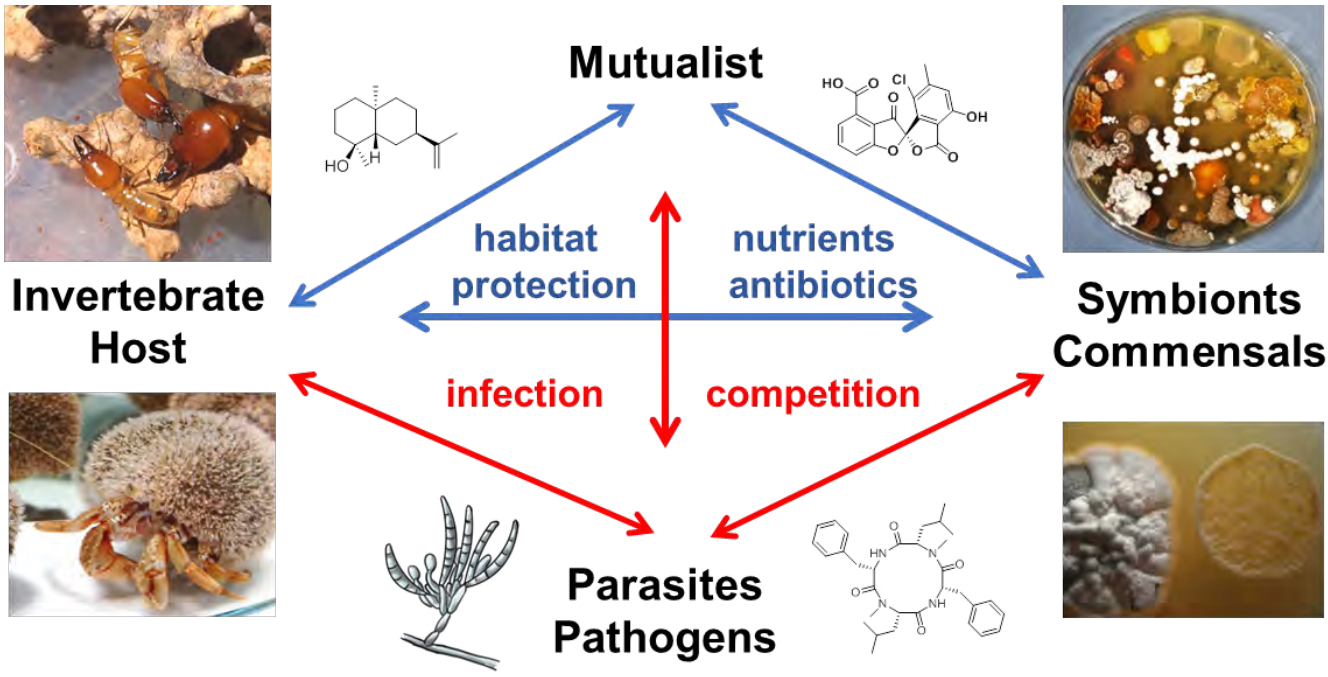


Figure: Within multi-partner associations, microbes secrete an array of chemically diverse small molecules to coordinate, influence and protect the system.

of these studies, linear and cyclic tetrapeptides (*Org Lett* 2016, *ChemBioChem* 2020) were identified and precursor-directed feeding experiments of synthetic and natural amino acids lead to the isolation of more than 20 new antimicrobial derivatives including homopropargyl-carrying derivatives (*ChemBioChem* 2018, Hot Paper). In parallel studies, the group investigated other co-isolated and entomophatogenic fungi and identified new phomaligadione-derived polyketide dimers, named beauvetetraones A-C (*Org Chem Front* 2018).

ception of bacterial morphogenic signals undergoes transformation into the mature organism. Using a bioassay-guided set-up, two different types of inducing compounds (*mBio*, accepted) were identified. Current efforts are also directed at synthesizing and modifying the inducing compounds (lipids and oligosugar) and elucidating their targets in *Hydractinia*. In parallel effort, novel sulfonolipids from marine bacteria were synthesized and identified, which differ in substitution pattern and stereochemistry and are known to be essential for bacterial physiology (*Org*

Biol Chem 2019). Amongst those, several structurally distinct sulfonolipids are known to induce morphogenesis in the eukaryote *Salpingoeca rosetta* (Choanoflagellate) (funded by DFG).

Based on microbial profiling studies of *Hydractinia* and genome-mining based approach, the group identified the first non-ribosomal peptide/ polyketide synthase hybrid gene clusters (PKS-NRPS) from an anaerobic Epsilonproteobacterium (*Sulfurospirillum barnesii*), a class which was previously not known to produce natural products. Based on these genome mining efforts, a novel modified lipo-dipeptide named barnesin A was identifed, and the absolute structure was verified by a modular total synthesis (*ACS ChemBio* 2018, *Org Lett* 2020). Barnesin and derivatives were found to have antimicrobial activity as well as selective and nanomolar inhibitory activity against pharmacological important cysteine proteases (patent application 2018). Based on a modified synthetic procedure, a barnesin library for activity studies is currently being established in collaboration with the Transfer group; a complementary molecular-biology oriented project has also being funded by the Boehringer Ingelheim Exploration Fund in 2019-2020. Cultivation-based approaches of *Hydractinina*-associated fungi, including *Cladosporium sphaerospermum* SW67, let to the isolation of new spirocyclic natural products named cladosporicin and cladosporiumins, which contain an unprecedented 2,7-diazaspiro[4.5]decane-1,4-dione skeleton conjugated with one 2,4-pyrrolidinedione moiety (tetramic acid) (*Org Chem Front*. 2018, *Mar Drugs* 2019).

Within the years 2018-2020, the group published 32 original articles and five review articles showing active collaborations with the FSU Jena (CRC ChemBioSys), within the Leibniz-HKI (Bio Pilot Plant, SMB, BMC) and internationally. Additional funding has been received by the ERC (Morpheus), DFG (BE4799/3-1), and the Boehringer Ingelheim Exploration Fund (2018-2019) and a newly launched subproject within the Cluster of Excellence Balance of the Microverse. Members of the group have given 46 talks on national and international symposia/conference, including 29 invited talks by Christine Beemelmanns. Overall one Bachelor, three Master students and two PhD students submitted and defended their thesis within 2018-2020. Christine Beemelmanns was been awarded the Otto-Röhm Gedächnis-Preis (2018) and the prestigious Goering-Visiting Professorship of the University of Madison-Wisconsin (USA, January to May 2020).

Selected collaborations

Cox, Russell
Leibniz University Hannover, Germany

De Beer, Wilhelm Z.
University of Pretoria, South Africa

Hadfield, Mike
University of Hawaii, Honolulu, USA

Hammerbach, Almut
University of Pretoria, South Africa

Jønsson, Knud Andreas
University of Copenhagen, Denmark

Kim, Ki Hyun
Sungkyunkwan University, Korea

King, Nicole
University of Berkley, USA

Poulsen, Michael
University of Copenhagen, Denmark

Werz, Oliver
Friedrich Schiller University Jena, Germany

Selected publications

1. Guo H, Schwitalla JW, Benndorf R, Baunach M, Steinbeck C, Görls H, de Beer ZW, Regestein L, Beemelmanns C (2020) Gene cluster activation in a bacterial symbiont leads to halogenated angucyclic maduralactomycins and spirocyclic actinospirols. *Org Lett* 22, 2634-2638.

2. Rischer M, Lee SR, Eom HJ, Park HB, Vollmers J, Kaster AK, Shin JH, Oh DC, Kim KH, Beemelmanns C (2018) Spirocyclic cladosporicin A and cladosporiumins I and J from a Hydractinia-associated *Cladosporium sphaerospermum* SW67. *Org Chem Front* 6 1084-1093.

3. Rischer M, Raguz L, Guo H, Keiff F, Diekert G, Goris T, Beemelmanns C (2018) Biosynthesis, synthesis and activities of barnesin A, a NRPS-PKS hybrid produced by an anaerobic Epsilonproteobacterium. *ACS Chem Biol* 13(8), 1990-1995.

4. Roman D, Raguž L, Keiff F, Meyer F, Barthels F, Schirmeister T, Kloss F, Beemelmanns C (2020) Modular solid-phase synthesis of antiprotozoal barnesin derivatives. *Org Lett* 22, 3744-3748.

5. Schalk F, Gostinčar C, Kreuzenbeck NB, Schantz-Conlon BH, Sommerwerk E, Rabe P, Burkhardt I, Krüger T, Kniemeyer O, Brakhage AA, Gunde-Cimerman N, De Beer WZ, Dickschat JS, Poulsen M, Beemelmanns C (2020) The termite fungal cultivar *Termitomyces* combines diverse enzymes and oxidative reactions for plant biomass conversion. *mBio*, accepted.

Major third party funding

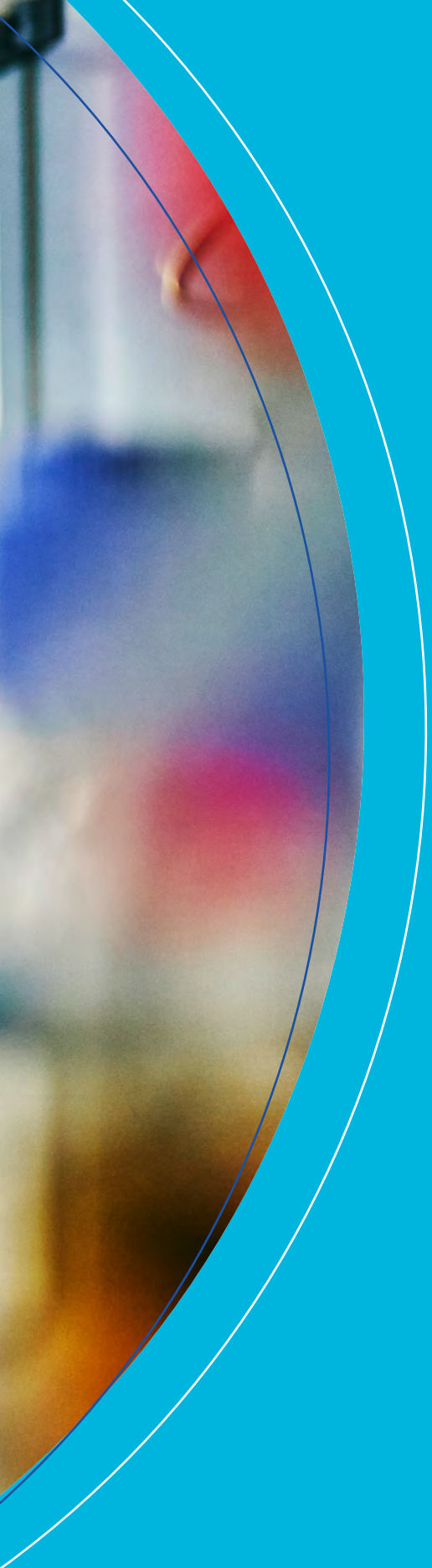
DFG: Cluster of Excellence Balance of the Microverse

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

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

EU: ERC Starting Grant MORPHEUS - Deciphering Bacteria-induced Morphogenesis and Protection in marine Eukaryotes

Boehringer Ingelheim Foundation: Engineering NRP-PKS-hybrid enzymes for production of y-Amino acids and unique products



LEIBNIZ-HKI

Independent
Junior Research Group

EVOLUTION OF MICROBIAL INTERACTIONS

EVOLUTION OF MICROBIAL INTERACTIONS

Mission

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.

Most important results

To study the influence of amoebae on the evolution of fungal pathogens the group has previously exploite the model amoeba *Dictyostelium discoiduem* (*Environ Microbiol* 2015; *Appl Microbiol Biotechnol* 2016; *Cell Chem Biol* 2016; *Front Cell Infect Microbiol* 2017). In the past two years the group has successfully isolated and characterized a fungi-only eating amoeba from the environment. As one of the very few members of the entire kingdom of the Amoebozoa, the genome of *Protostelium aurantium var. fungiv-*

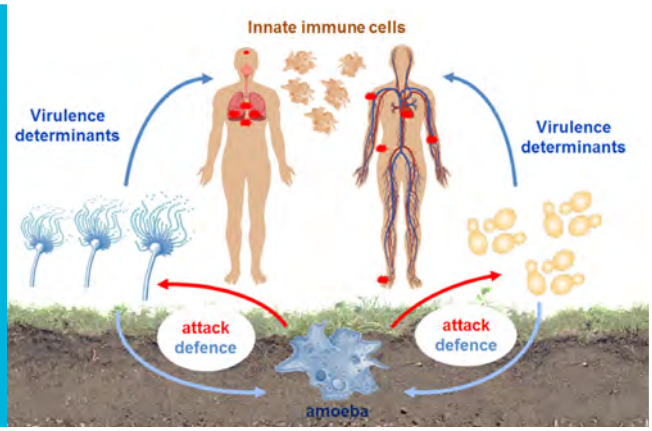


Figure: Predation by mycophagous amoeba could have imposed a selection pressure on environmental fungi to acquire traits which have later supported resistance to innate immune cells.

orum was sequenced and fully annotated through a highly collaborative effort involving groups from Jena (Leibniz-HKI and FSU Jena), Cologne and Dundee, Scotland. The JSMC doctoral students Silvia Radosa and Iuliia Ferling made significant contributions to this publication (*Genome Biol Evol* 2018).

During this time the group has successfully adapted *P. aurantium* to standard laboratory techniques and can now culture the organism in large scales requiring essentially only a fungal food source which can be either acomycetous or basidimycetous yeasts or even human pathogens. The very unique feeding mode on fungal hyphae, which are actively invaded through a perforation of the cell wall was discovered by Iuliia Ferling (*Environ Microbiol* 2019). We coined the new feeding mechanism "ruphocytosis" (rupho-, greek, "to suck" or "to slurp"). In an EMBO supported collaboration with Thierry Soldati, Geneva, Iuliia Ferling has further delineated the intracellular processing mechanisms of *A. fumigatus* conidia in *D. discoideum* (*mBio* 2020). Silvia Radosa investigated the fungal response to the predator. Here, the group had internal collaborations with Gianni Panagiotou (SBI), Sascha Brunke (MPM) and externally with Attila Gaçser (University of Szeged, Hungary).

Both, Iuliia Ferling and Silvia Radosa have submitted and defended their dissertations. With support of a newly acquired DFG grant and a JSMC fellowship, the group aims to identify a cytolytic peptide of *P. aurantium* which causes fungal lysis. As the group is highly interested in expanding the range of new imaging techniques, as the nanoscale imaging of subcellular structures with XUV light, there is an ongoing collaboration with two groups from the Helmholtz Institute Jena (HIJ) within the Leibniz Science Campus InfectoOptics, supported by a one-year start up grant from the FSU.

With support of the European Social Fund ESF, the doctoral student Christin Reimer has developed a molecular platform to produce thus-far inaccessible polyketides based on natural products from *D. discoideum*. She was recently awarded the prize for the best poster presentation at the international symposium on the genetics of industrial microrganisms

(GIM 2019, Pisa, Italy). The work involves an active collaboration with the two Junior Research Groups of Vito Valiante and Pierre Stallforth. First bioreactor cultivations with *D. discoideum* for the production of new polyketides have been successfully carried out in the BioPilot Plant (Lars Regestein). In 2020 the group acquired BMBF funding within the GoBio initial initiative and the results have undergone a patent application.

Selected collaborations

Gacser, Attila
University of Szeged, Hungary

Hagemann, Martin
University of Rostock, Germany

May, Robin
University of Birmingham, UK

Rothardt, Jan
Helmholtz Institute Jena, Germany

Soldati, Thierry
University Genf, Switzerland

Schaap, Pauline
University of Dundee, UK

Selected publications

1. Ferling I, Dunn JD, Ferling A, Soldati T, Hillmann F (2020) Conidial melanin of the human pathogenic fungus *Aspergillus fumigatus* disrupts cell autonomous defenses in amoebae. *mBio* 11, e00862-20.

2. Hillmann F, Forbes G, Novohradská S, Ferling I, Riege K, Groth M, Marz M, Spaller T, Winckler T, Schaap P, Gloeckner G (2018) Multiple roots of fruiting body formation in Amoebozoa. *Genome Biol Evol* 10, 591-606.

3. Janevska S, Ferling I, Jojić K, Rautschek J, Hoefgen S, Proctor RH, Hillmann F, Valiante V (2020) Self-protection against the sphingolipid biosynthesis inhibitor fumonisin B1 is conferred by a FUM cluster-encoded ceramide synthase. *mBio* 11, e00455-20.

4. Noßmann M, Pieper J, Hillmann F, Brakhage AA, Munder T (2018) Generation of an arginine-tRNA-adapted *Saccharomyces cerevisiae* strain for effective heterologous protein expression. *Curr Genet* 64, 589-598.

5. Radosa S, Ferling I, Sprague JL, Westermann M, Hillmann F (2019) The different morphologies of yeast and filamentous fungi trigger distinct killing and feeding mechanisms in a fungivorous amoeba. *Environ Microbiol* 21, 1809-1820.

Major third party funding

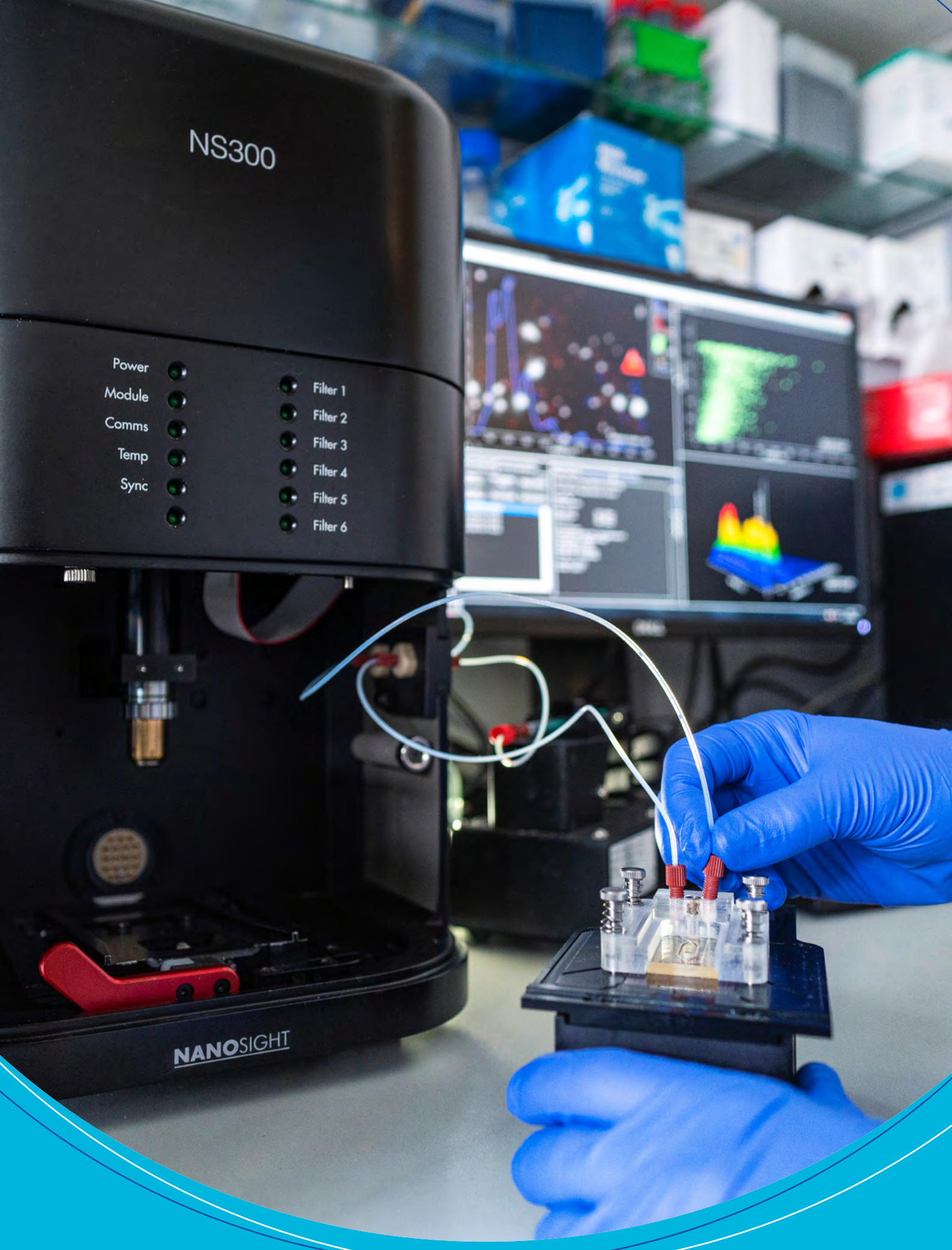
DFG Cluster of Excellence Balance of the Microverse

DFG Research Grant: Molekulare Muster zur Erkennung und Diskriminierung von Pilzen während der Phagozytose durch räuberische Amöben

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

BMBF: GO-bio Initial PRoDICAN - Produktion von Cannabinoiden in *Dictyostelium discoideum*

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

Independent
Junior Research Group

RNA BIOLOGY OF FUNGAL INFECTIONS

RNA BIOLOGY OF FUNGAL INFECTIONS

Mission

We are particularly interested in the detection of RNA populations in host extracellular vesicles that are produced in response to an infection and that can serve as possible diagnostic markers. In addition, we are working to advance our understanding of fungal non-coding RNAs and RNA-binding proteins to facilitate the advancement of new targets for RNA-based therapeutics.

Most important results

The Independent Junior Research Group RNA Biology of Fungal Infections (RBI) was established on November 1st, 2020 after a successful application to a call from the *Bundesministerium für Bildung und Forschung* (BMBF) for new Junior Research Groups in Infection Biology.

The primary research goal of the RBI group is to explore the potential of RNA in the treatment and diagnosis of life-threatening fungal infections. Diagnosis remains slow, resistance to available treatment regiments is increasing, and new therapeutic interventions are desperately needed to treat fungal infections. As observed with the recent successful vaccines against SARS-CoV-2, RNA-based therapeutics are emerging as important weapons against infectious diseases. Unfortunately, fungal infections remain exceptionally challenging to treat and diagnosis due to their high genetic similarity to humans and their ubiquitous nature. RNA-based therapeutics offer a previously underappreciated source of potential interventions, but the robust fungal cell wall often prevents uptake of exogenous RNA. In terms of diagnosis, fungal infections are often confirmed too late for effective treatment due to limited sample availability. The first experiments in the lab have started to address these problems from two directions.

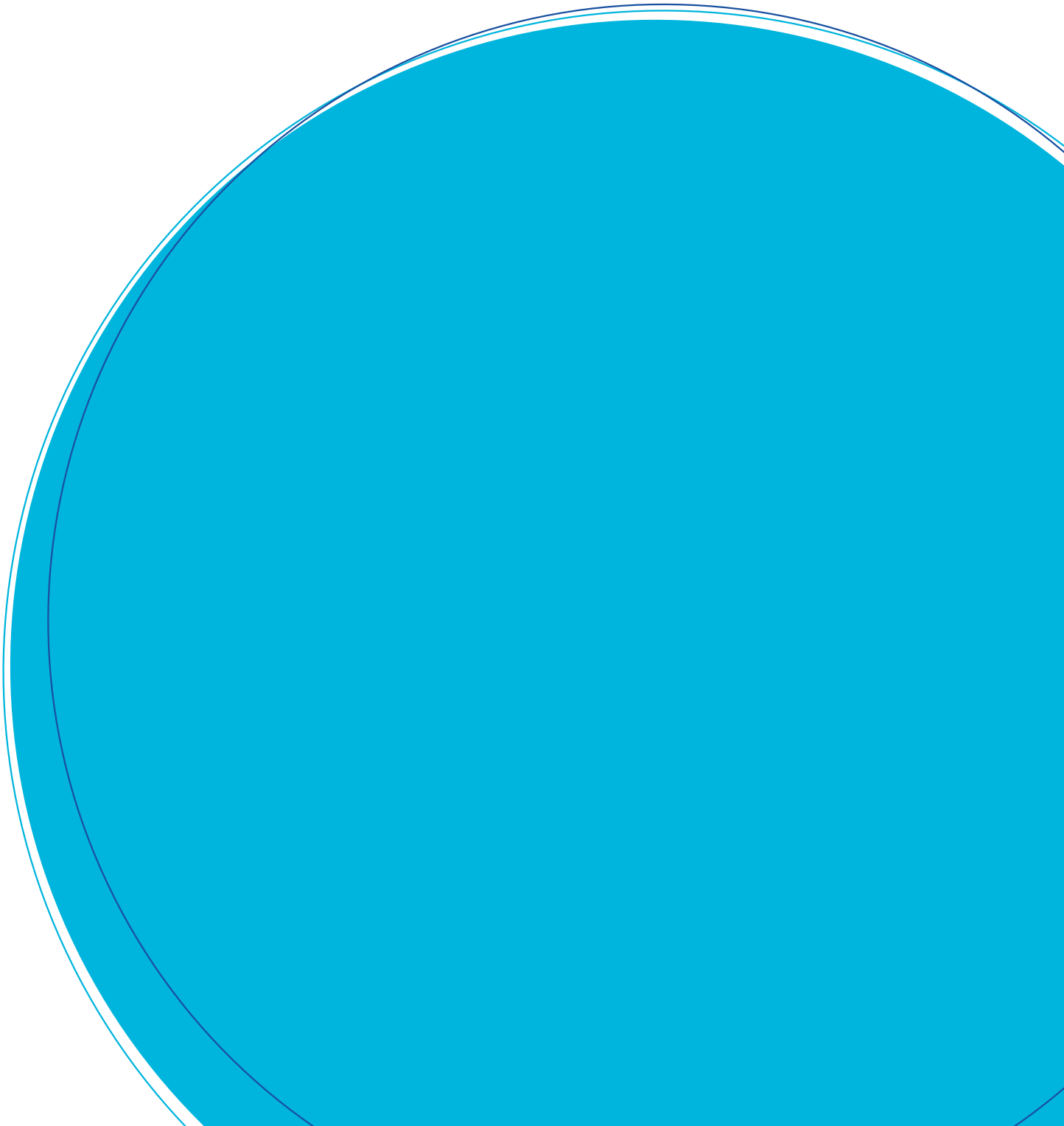
Our new postdoc, Alexander Bruch, is investigating the contribution of extracellular RNA produced by monocytes and neutrophils in response to fungal infection. The ultimate goal is to identify RNA populations within extracellular vesicles that might be used for potential diagnosis of fungal infections. Due to their enhanced stability, potential for amplification, and potential pathogen specificity, RNA encased in vesicles offers a unique opportunity to assess host status. Samples are currently being prepared in collaboration with two local groups (Kai Papenfort and Kathrin Fröhlich) at the Friedrich Schiller University in Jena (FSU Jena) to define the RNA population in host EVs in response to infection.

The second focus of our initial research has been to better define the non-coding RNA pathways of important human pathogens like *Aspergillus fumigatus*. In a manuscript that is nearing preparation, our PhD student, Abdulrahman Kelani, has created a series of knockouts of the fungal RNAi machinery, and investigated the contributions of these enzymes to gene silencing and growth. This work is being done in collaboration with the group of Axel Brakhage at the Leibniz-HKI, and the groups of Michael Bromley and Paul Bowyer at the University of Manchester, UK. We have also sequenced the small RNA population of Aspergillus fumigatus and are working in collaboration with the group of Manja Marz – FSU Jena) to better characterize these RNAs. In addition, we are trying to set up several systems to quantitatively track the interkingdom transfer of RNA between host and pathogen using a series of molecular tools, including a CRISPR-Cas9 Spotlight approach.

Ultimately, we hope to increase our knowledge of how RNA is regulated during fungal infection to provide additional targets for potential therapeutic intervention, as well as unique diagnostic approaches.

Major third party funding

BMBF: Junior Research Group RFIN – RNA-Biologie von Pilzinfektionen



Independent Junior Research Group
SYNTHETIC MICROBIOLOGY

SYNTHETIC MICROBIOLOGY

Mission

Our mission is the discovery and characterization of novel bioactive molecules and their use in synthetic biology. We focus on unusual cofactors of pathogenic bacteria that might represent drug targets and can be exploited for biocatalysis and bioelectrochemical applications. We furthermore develop therapeutic microbes, i.e., probiotic bacteria that are engineered to diagnose diseases and counteract pathogens by the production of pharmaceuticals.

Most important results

Our research interests are **novel roles and applications of bacterial natural products.** We investigate unusual redox cofactors and develop natural products as tools for therapeutic microbes.

Unusual Cofactors: We are convinced that an interesting and long-overlooked function of cryptic natural products is their potential role as **cofactors**. Unusual cofactors like coenzyme F_{420} promise valuable applications in biocatalysis and represent interesting targets for the development of **novel antibiotics**, especially against pathogenic mycobacteria like *Mycobacterium tuberculosis*. We therefore investigate their biosynthesis, biochemical function, and biotechnological application of unusual cofactors. We conduct biochemical characterization of cofactors and their dependent **enzymes** and develop efficient regeneration systems for these cofactors.

As one model system, we investigate novel roles and functions of **coenzyme F_{420}** in underexplored contexts. For instance, we investigate the role of F_{420} in bacterial-fungal symbiosis in a joint project with the Hertweck lab. We successfully collaborate with the Beemelmanns group for structure elucidation studies of novel F_{420}- derivatives and with the Rosenbaum group to assess the function of redox-active molecules as redox mediators. Furthermore, we design synthetic operons to enable cofactor formation in model organisms. Together with Lars Regestein (Bio Pilot Plant), we optimize cofactor production on large scale. Crystallographic studies of F_{420}-dependent enzymes are currently performed in collaboration with Michael Lammers (University of Greifswald).

As a next step, we aim at the discovery of **novel cofactors by genome mining and metabolomics.** Particularly, we have discovered the novel cofactor **mycofactocin**. Mycofactocin is crucial for the physiological plasticity of pathogenic mycobacteria, for instance for growth on ethanol.

Therapeutic Microbes: We develop therapeutic microbes, i.e., probiotic bacteria whose health benefits are enhanced by synthetic biology. Our vision is to couple biosynthetic gene clusters of bioactive molecules with microbial biosensors, specific adhesion molecules, and other cellular communication tools in commensal bacteria such as *Escherichia coli* Nissle 1917. The therapeutic bacteria produced in this way live within the human microbiome, recognize diseases, and react as required with the synthesis of therapeutics directly at the site of action (e.g. tumors or pathogens). A pilot study on the engineering of **synthetic, antifungal bacteria** is being carried out as a project within the Jena School for Microbial Communication (JSMC). Using *Candida albicans* as a model target, this work is a close collaboration with the group of I. Jacobsen at the Leibniz-HKI. A follow-up project is supported by the DFG Cluster of Excellence Balance of the Microverse that focuses on the development of surface recognition and adhesion of therapeutic microbes to pathogens. A follow-up project will be financed by the BMBF within the Leibniz Center for Photonics in Infection Research (LPI) and is designed to bring this technology into use.

Selected Results

In the course of our project on coenzyme F_{420}, we discovered **new coenzyme F_{420} derivatives** (3PG-F_{420}) produced by endofungal bacteria living within fungal hyphae (Braga *et al.*, *ACS Chem Biol* 2019). We showed together with the group of Christine Beemelmanns and Christian Hertweck that F_{420} is produced during bacterial-fungal symbiosis. Intriguingly, the novel cofactor is not restricted to this particular ecological niche but was also found in a biogas production plant. By extensive genetics studies and biochemical assays, we could demonstrate that a substrate specificity switch in a key biosynthetic enzyme (CofC) was accountable for the production of the novel cofactor for F_{420}-dependent biosynthetic gene clusters. We could furthermore elucidate a critical step of the **F_{420} biosynthesis in thermophilic bacteria** and thus shed light on the evolution of enzymes involved in this process (Braga *et al.*, *Appl Environ Microbiol* 2020).

Our efforts to identify the novel mycobacterial cofactor mycofactocin have made significant progress. Using an integrated **metabolomics workflow** based on high-resolution mass spectrometry we identified **mycofactocins** for the first time in cells of living bacteria (model system: *Mycolocibacterium smegmatis*). Structure elucidation in collaboration with the Beemelmanns lab and T. Köllner from the MPI-CE Jena revealed that naturally occurring mycofactocins

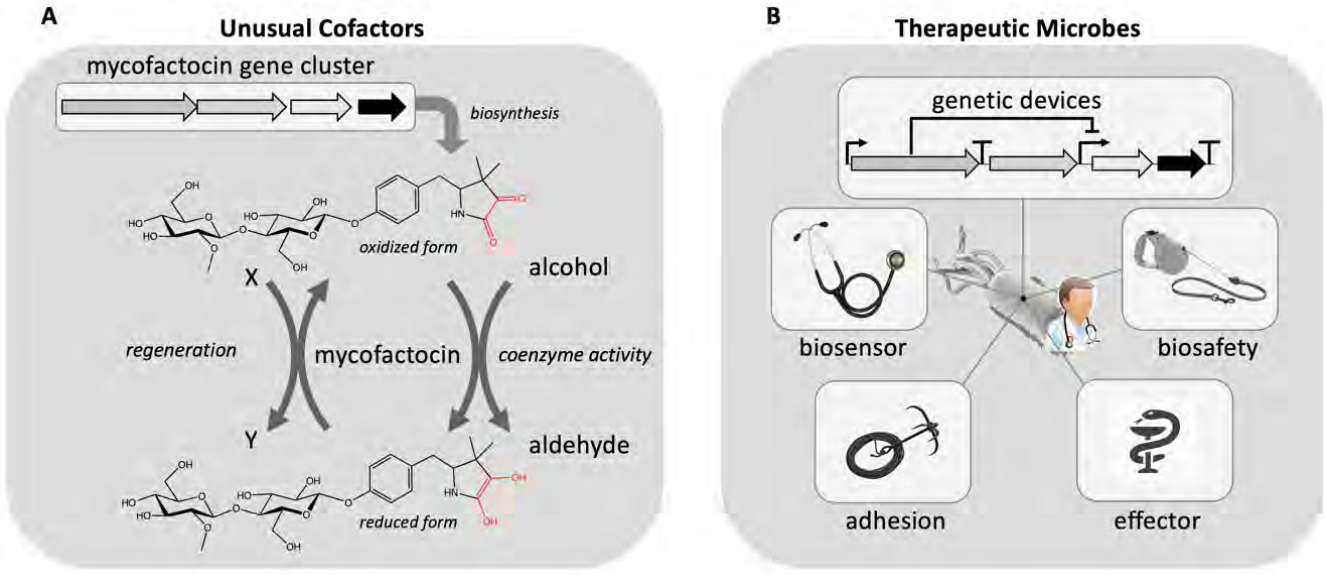


Figure: Mission and aims of the junior research group SMB. A) Discovery and characterization of unusual cofactors as exemplified by the mycobacterial cofactor mycofactocin. Mycofactocin is reduced and regenerated during alcohol metabolism. B) The development of probiotic bacteria into therapeutic microbes follows a modular design.

derivatives. This switch made it feasible to produce 3PG-F_{420} in the model bacterium *E. coli*. After being able to produce F_{420}-derivatives in our engineered *E. coli* strain, we successfully used this strain to conduct **whole-cell biocatalysis**. We currently investigate the synthetic *E. coli,* e.g., as an expression host are glycosylated and exist in reduced and oxidized forms in the cell (Peña-Ortiz *et al. Chem Sci* 2020). This discovery was published in the renowned journal *Chemical Science* and was awarded the Medac Forschungspreis 2020 as well the Leibniz Drug of the Year Award 2021. In a follow-up study with Lars

Regestein we evaluated parameters for large-scale production of mycofactocin (Peña-Ortiz *et al.*, *Front. Bioeng Biotechnol* 2020).

Apart from the cofactor project, we are involved in projects addressing other natural products. One major success was the characterization of the blueing reactions of hallucinogenic mushrooms, a group of mushrooms also known as "magic mushrooms." Once the mushrooms are injured, enzymes trigger the formation of blue polymers that repel insects that feed on the fruiting bodies. Using mass spectrometry, we assisted the group of Dirk Hoffmeister in identiying the enzymes involved in this process (Lenz *et al.*, *Angew. Chem. Int. Ed.* 2020).

Outlook: After the discovery of mycofactocin, we initiated a collaboration with Ivan Vilotijevic (FSU). His group is skilled in sugar chemistry and will conduct the chemical synthesis of mycofactocin derivatives. We are writing a **joint DFG proposal** to further study the biochemistry, biosynthesis, structural diversity and function of mycofactocins. We are currently investigating natural regeneration systems of mycofactocin in *M. smegmatis* and teamed up with the Friedrich Loeffler Institute in Jena to investigate the occurrence of mycofactocin in *M. tuberculosis*.

The project on therapeutic microbes is ongoing. We have, however, successfully produced antifungal molecules and potential anti-virulence factors against *C. albicans* in *E. coli* Nissle 1917. We are now optimizing the antifungal activity of engineered strains. A platform for rapid cloning, assembly, and genome integration of genetic devices in *E. coli* Nissle is being developed. The next step will be the coupling of antifungal molecule production with a biosensor against *C. albicans* and the development of adhesion devices to enhance the binding of therapeutic microbes to pathogenic fungi. For the latter project, Alexandre Chamas has joined the group in 2020 to engineer surface interactions of *E. coli* with *C. albicans*. In the future, we will conduct further Design-Build-Test cycles to optimize the strains obtained. One novel focus of development is the biosafety of engineered microbes. General future strategies comprise the following aspects.

Improvement of single functions (modules) included in a Therapeutic Microbe, e.g., production of bioactive molecules, adhesion devices, biosafety modules biosensors.

Integration of modules to obtain strains with emerging properties

Testing Therapeutic Microbes in increasingly complex environments, e.g. switchable surfaces (collaboration with Lothar Wondraczeck) or tissue models and *in-vivo* models (collaboration I. Jacobsen)

Transfer of technology to further chassis organisms (e.g., *Saccharomyces* spp.)

Selected publications

1. Braga D, Hasan M, Kröber T, Last D, Lackner G (2020) Biosynthesis of the redox coenzyme F420 in Thermomicrobia involves reduction by standalone nitroreductase superfamily enzymes. *Appl Environ Microbiol* 86(12), e00457-20.

2. Lenz C, Wick J, Braga D, Garcia-Altares M, Lackner G, Hertweck C, Gressler M, Hoffmeister D (2020) Injury-triggered blueing reactions of *Psilocybe* "magic" mushrooms. *Angew Chem Int Ed* 59(4), 1450-1454.

3. Peña-Ortiz L, Graça AP, Guo H, Braga D, Köllner TG, Regestein L, Beemelmanns C, Lackner G (2020) Structure elucidation of the redox cofactor

mycofactocin reveals oligo-glycosylation by MftF. *Chem Sci* 11, 5182-5190.

4. Peña-Ortiz L, Schlembach I, Lackner G, Regestein L (2020) Impact of oxygen supply and scale up on *Mycobacterium smegmatis* cultivation and mycofactocin formation. *Front Bioeng Biotechnol* 8(1399), 593781.

5. Braga D, Last D, Hasan M, Guo H, Leichnitz D, Uzum Z, Richter I, Schalk F, Beemelmanns C, Hertweck C, Lackner G (2019) Metabolic pathway rerouting in *Paraburkholderia rhizoxinica* evolved long-overlooked derivatives of coenzyme F420. *ACS Chem Biol* 14(9), 2088-2094.

Selected collaborations

Hoffmeister, Dirk
FSU Jena, Germany

Köllner, Tobias
MPI-CE, Jena, Germany

Lammers, Michael
University of Greifswald, Germany

Major third party funding

DFG: Cluster of Excellence Balance of the Microverse

DFG: Neue Wege in der Cofaktor-Forschung: Entdeckung und Entwicklung Coenzym F420-abhängiger Bioprozesse

Cross-sectional Unit

INTERNATIONAL LEIBNIZ RESEARCH SCHOOL FOR MICROBIAL AND BIOMOLECULAR INTERACTIONS (ILRS)

INTERNATIONAL LEIBNIZ RESEARCH SCHOOL FOR MICROBIAL AND BIO-MOLECULAR INTERACTIONS (ILRS)

Mission

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.

Most important results

The *International Leibniz Research School for Microbial and Biomolecular Interactions* (ILRS) as graduate school of the Leibniz-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, more than 70 doctoral researchers from 19 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 Leibniz-HKI benefit from the structured graduate training.

Figure 1: ILRS and JSMC doctoral researchers Stefanie Allert, Mariana Murillo-Roos and Jens Esken discuss career perspectives during the World Café at the Alumni Meeting.

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) and the Jena Alliance of Graduate Schools "Life in Focus". In June 2019, ILRS and JSMC together organized the second Alumni Meeting at the Leibniz-HKI. Former graduates talked about their jobs in academia or industry and discussed career prospects with current members of the two graduate schools.

For the second time, the annual ILRS Symposium 2019 took place as first Joint Meeting together with the Research Training Group (RTG) 1870: Bacterial Respiratory Infections from the University of Greifswald. Doctoral researchers and Faculty members met at the Leucorea in Lutherstadt Wittenberg to present and discuss their research projects.

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 Scientific Advisory Board

Prof. Gerhard Bringmann (Julius-Maximilians-Universität Würzburg)

Prof. Sven Hammerschmidt (Ernst-Moritz-Arndt-Universität Greifswald)

Prof. Petra Dersch (Helmholtz-Zentrum für Infektionsforschung, Braunschweig)

Prof. Kristian Riesbeck (Lund University, Schweden)

ILRS Steering Committee

Peter F. Zipfel (Spokesperson, Leibniz-HKI, Infection Biology)

Ian T. Baldwin (Max Planck Institute for Chemical Ecology)

Christine Beemelmanns (Leibniz-HKI, Chemical Biology of Host-Microbe Interactions)

Gabriele Diekert (Friedrich Schiller University)

Berhard Hube (Leibniz-HKI, Microbial Pathogenicity Mechanisms)

Dirk Hoffmeister (Friedrich Schiller University)

ILRS Representatives

Vivien Hotter (Friedrich Schiller University)

Dolly Montano (Leibniz-HKI, Jena Microbial Resource Collection)

Figure 2: Joint Meeting of doctoral researchers and faculty members from ILRS Jena and RTG 1870 from Greifswald at the Leucroea, Lutherstadt Wittenberg.

JMRC

Cross-sectional Unit

JMRC – JENA MICROBIAL RESOURCE COLLECTION

JMRC – JENA MICROBIAL RESOURCE COLLECTION

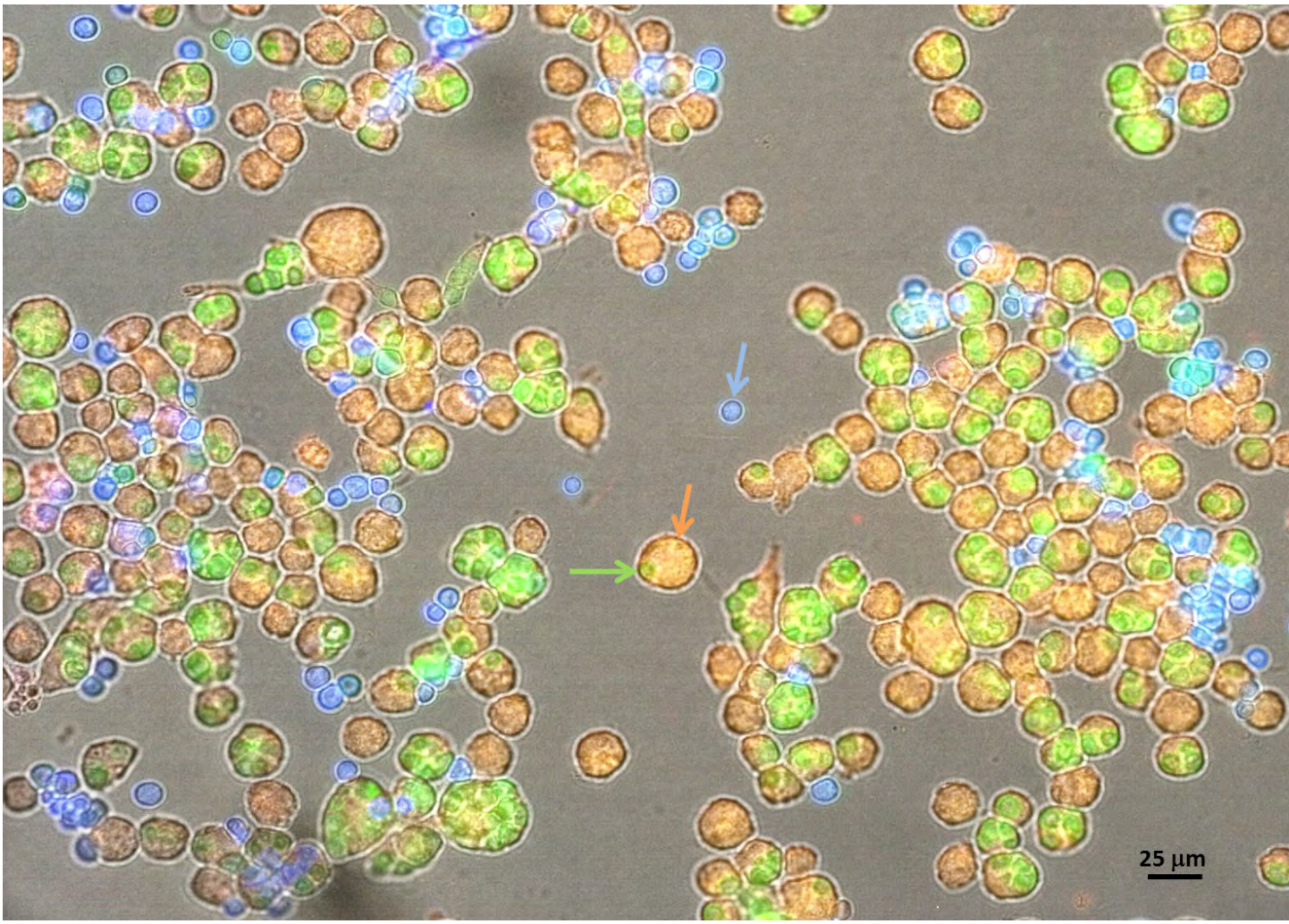
Mission

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.

Most important results

Mucormycosis is a life-threatening disease that affects in particular immune-deficient patients. Two strains of *L. corymbifera* species 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 plays 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 the attenuated strains was observed. The hydrophobic surface binding protein A (HsbA) ranges among the most abundant ones. 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 the genome of *L.corymbifera*, a total of four copies of the gene encoding the HsbA protein were identified and heterologously overexpressed in *Pichia pastoris*. Polyclonal and monoclonal antibodies 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 flow cytometry (FC) and confocal laser scanning (CLSM) microscopy. HsbA proteins bind to monocytes and macrophages and have the capability of blocking the phagocytic processes during the interaction of *Lichtheimia* spores with macrophages. 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 play a detectable role in this process. Moreover, we found that HsbA proteins don't influence the intraphagocytic acidification processes. But, HsbA appears to be secreted by the fungus in the surrounding host tissue as shown in infected murine lung tissue MALDI-imaging combined with immune histochemical visualization. Furthermore, we have elucidated the role of iron assimilation and iron storage during phagocytosis of *L. corymbifera* and found that the iron permease FTR1 exists in multiple copies which are syntenic to the multicopper oxidase FET3. Overexpression of single FTR1 copies in yeast and subsequent confrontation of the mutants to macrophages revealed possible functions of FTR1-II and FTR1-IV in the recognition by professional phagocytes. From the host side, we also identified the heat-shock protein HspA8 as potential receptor that may contribute to recognition and subsequent adherence of the spores to the macrophage surface. Our studies will have remarkable contribution to the understanding of the interaction of mucoralean fungi with professional phagocytes which comprise the first line of defenseof the innate immune system against fungal infections.

Figure: *In vitro* interaction of spores of the human pathogenic fungus *Lichtheimia corymbifera* with murine alveolar macrophages as shown by confocal laser scanning microscopy. The internal (phagocytosed) spores are indicated in green, the external (adherent) spores are shown in blue. The macrophages are shown in orange. Arrows in green, blue and orange ascribe to individual cases of internal, external spores and macrophages, respectively.



Selected publications

Hassan MIA, Keller M, Hillger M, Binder U, Reuter S, Herold K, Telagathoti A, Dahse HM, Wicht S, Trinks N, Nietzsche S, Deckert-Gaudig T, Deckert V, Mrowka R, Terpitz U, Saluz HP, Voigt K (2021) The impact of episporic modification of *Lichtheimia corymbifera* on virulence and interaction with phagocytes. *Comput Struct Biotechnol J* 19, 880-896.

Stanford FA, Matthies N, Cseresnyés Z, Figge MT, Hassan MIA, Kerstin Voigt (2021) Expression patterns in reductive iron assimilation and functional consequences during phagocytosis of *Lichtheimia corymbifera*, an emerging cause of mucormycosis. *J Fungi* 7(4), 272.

Böttcher S, Hartung S, Meyer F, Rummler S, Voigt K, Walther G, Hochhaus A, von Lilienfeld-Toal M, Jahreis S (2021) Human mucosal-associated invariant T cells respond to Mucorales species in a MR1-dependent manner. *Med Mycol* 59(5), 505-509.

Hassan MIA, Kruse JM, Krüger T, Dahse HM, Cseresnyés Z, Blango MG, Slevogt H, Hörhold F, Ast V, König R, Figge MT, Kniemeyer O, Brakhage AA, Voigt K (2020) Functional surface proteomic profiling reveals the host heat-shock protein A8 as a mediator of *Lichtheimia corymbifera* recognition by murine alveolar macrophages. *Environ Microbiol* 22(9), 3722-3740.

Montaño DE, Voigt K (2020) Host immune defense upon fungal infections with mucorales: Pathogen-immune cell interactions as drivers of inflammatory responses. *J Fungi* 6(3), E173. (Review)

Stanford FA, Voigt K (2020) Iron assimilation during emerging infections caused by opportunistic fungi with emphasis on Mucorales and the development of antifungal resistance. *Genes (Basel)* 11(11), E1296. (Review)

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

DAAD: Adaptive traits as mediators of stress response and virulence in *Lichtheimia*

Cross-sectional Unit

TRANSFER GROUP ANTIINFECTIVES

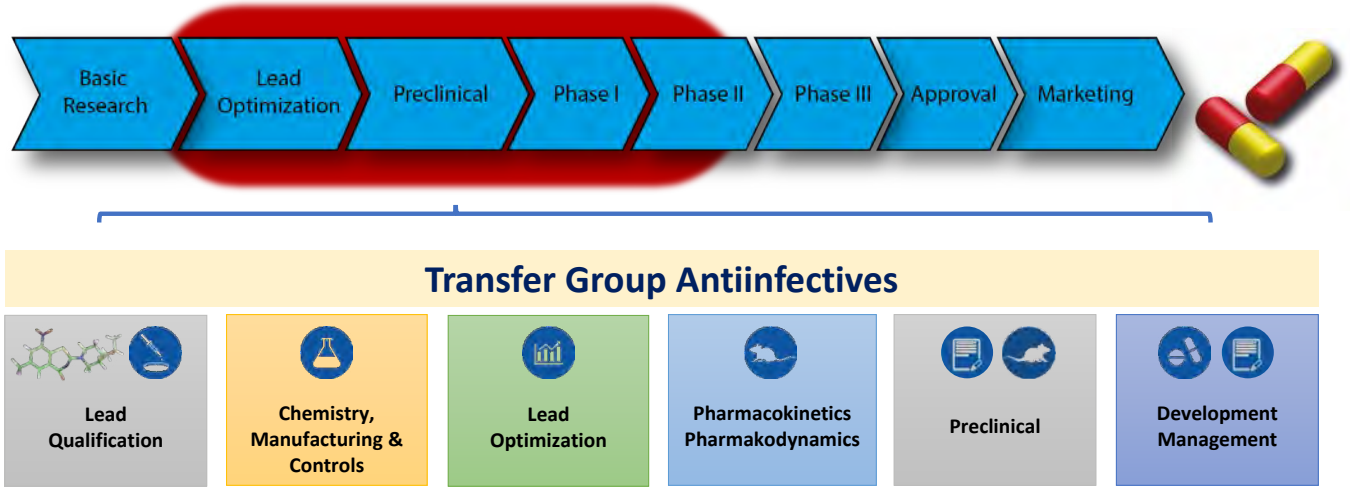
TRANSFER GROUP ANTIINFECTIVES

Mission

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.

Most important results

The successful development of antimicrobials requires a sustainable pipeline filled with compounds at different progress stages from discovery to the clinic. In the course of our recent activities, many new compounds from different academic partners and



of active projects increased, seven substance classes were terminated as target lead profiles could not be met based on multidimensional ADME-PK-, Tox-, *In-vivo*- or safety testing. Compared to earlier years, it is obvious that the increased throughput of our lead qualification process was drastically improved within 2020 and key to a more sophisticated de-risking and decision-making process on compounds from medicinal chemistry programs or natural product projects.

For the appropriate profiling of compounds, a series of pharmacological assays with a focus on metabolic stability, permeation behavior and dissolution properties were implemented and/or significantly improved. Furthermore, as part of the in vivo testing, new methodologies were evaluated to combine classical pharmacokinetic studies with extensive DMPK-studies in a way that the quality of results could be significantly improved while the numbers of animals required could even be reduced successfully. In this regard, the earlier established bioanalytical HRMS platform was developed towards minimalistic sample sizes and sophisticated targeted and untargeted workflows for metabolite identification were constructed and qual-

Leibniz-HKI units were constantly evaluated in terms of antimicrobial activities, cell line toxicity, physicochemical and pharmacological parameters. On this basis scaffolds with potential antifungal, anti-mycobacterial, and most recently, antiSARSCoV2 activity were identified, which entered several medicinal chemistry endeavors within our group. Doing so, the TTA was able to expand the Leibniz-HKI development pipeline from thirteen to seventeen ongoing small molecule programs. While the overall number

ified. Although laboratory work in 2020 was heavily affected by the corona-crisis, this situation catalyzed a very positive structural development regarding our workflows and level of standardization and ultimately, sets the stage for prolific internal collaborations. External collaborations were also stimulated during the lockdown period as antiviral compounds were increasingly sought after by academic groups. With the aim to improve compound logistics and management, we introduced a new front end of the HKI substance library by early 2020 where all new compounds and testing data can easily be maintained by PIs of HKI internal groups. Furthermore, the HKI natural product collection was revisited as screening capacities grew.

Substantial efforts of the TTA are dedicated to the development of the benzothiazinone BTZ-043, a first in class anti-mycobacterial antibiotic first discovered at the Leibniz-HKI. Our team and project partners were able to acquire funding of over 18 Mio € to perform all required non-clinical and clinical studies until clinical phase IIb/c. Fortunately, the ongoing clinical phase II study in South Africa could be pursued despite corona restrictions, albeit with reduced pace. Interims data showed a good and dose dependent early bactericidal activity of BTZ-043. This milestone was an important de-risking step for the overall development and strongly encourages proceeding with all upcoming pricy studies. This particularly applies to the hADME study, the long-term toxicology study in minipigs and the reproduction toxicology package. As to the nonclinical investigations around BTZ-043, a significant effort was spent during 2020 towards the investigation of the drug-drug-interactions potential. A broad panel of drug transporters were analysed regarding their inhibition by main metabolites of BTZ-043, for which now selective chemical approaches could be developed. Furthermore, formulation development for a radioactive human formulation was initiated together with PRA health sciences. With regard to potential combination partners in the clinic, several animal studies were performed in 2020 at the Leibniz-HKI as well as at partner sites.

Within recent years the TTA could grow to 12 full-time-members. In the two years, we plan to expand our expertise in PK/PD also with a focus towards innovative therapeutic concepts such as life therapeutics. Furthermore, we plan to increase testing capacities and capabilities through implementation of an integrated robotics platform in 2021-22. We intend a further build-up of ten FTEs in line with the needs of our future discovery and development programs.

Selected collaborations

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Gabriel, Gülsah
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Gasteiger, Georg
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Müller, Uwe
HAPILA GmbH, Gera

Schubert, Ulrich
Friedrich Schiller University, Jena, Germany

Selected publications

1. Blei F, Dörner S, Fricke J, Baldeweg F, Trottmann F, Komor AJ, Meyer F, Hertweck C, Hoffmeister D (2020) Simultaneous production of psilocybin and a cocktail of β-carboline monoamine oxidase inhibitors in 'magic' mushrooms. *Chem Eur J* 26(3), 729-734.

2. Dunbar KL, Dell M, Molloy EM, Kloss F, Hertweck C (2019) Reconstitution of iterative thioamidation in closthioamide biosynthesis reveals a novel non-ribosomal peptide backbone-tailoring strategy. *Angew Chem Int Ed* 58, 13014-13018.

3. Kloss F, Neuwirth T, Haensch VG, Hertweck C (2018) Metal-free synthesis of pharmaceutically important biaryls by photosplicing. *Angew Chem Int Ed* 57, 14476-14481.

4. Manfiolli AO, Siqueira FS, Dos Reis TF, Van Dijck P, Schrevens S, Hoefgen S, Föge M, Straßburger M, de Assis LJ, Heinekamp T, Rocha MC, Janevska S, Brakhage AA, Malavazi I, Goldman GH, Valiante V (2019) Mitogen-activated protein kinase cross-talk interaction modulates the production of melanins in *Aspergillus fumigatus*. *mBio* 10, pii: e00215-19.

5. Roman D, Raguž L, Keiff F, Meyer F, Barthels F, Schirmeister T, Kloss F, Beemelmanns C (2020) Modular solid-phase synthesis of antiprotozoal barnesin derivatives. *Org Lett* 22(10), 3744-3748.

Major third party funding

Free State of Thuringia (ESF): Next-Gen-BTZ; Entwicklung einer nächsten Generation von Antituberkulotika durch Metabolismus-geleitete Leitstruktur-Optimierung von Benzothiazinonen

Free State of Thuringia (EFRE): Aufbau einer zielgerichteten Prozessierungslinie zur Auffindung und frühen Erprobung neuer antibiotischer Wirkstoffe - Drug-Development-Package

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

BMBF InfectControl: New antiinfection strategies – Science • Society • Economy – Drug Development Project

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

LEIBNIZ-HKI

Associated Group

HOST-FUNGAL-INTERFACES

HOST-FUNGAL-INTERFACES

Mission

Host Fungal Interfaces has been established within the ZIK Septomics to investigate adaptation mechanisms of *Candida albicans* to the dynamic and diverse host environments. In *C. albicans* such adaptations are driven by complex regulatory networks that link metabolism, responses to environmental stressors and expression of virulence characteristics, all contributing to the successful colonization and pathogenicity of the fungus.

Most important results

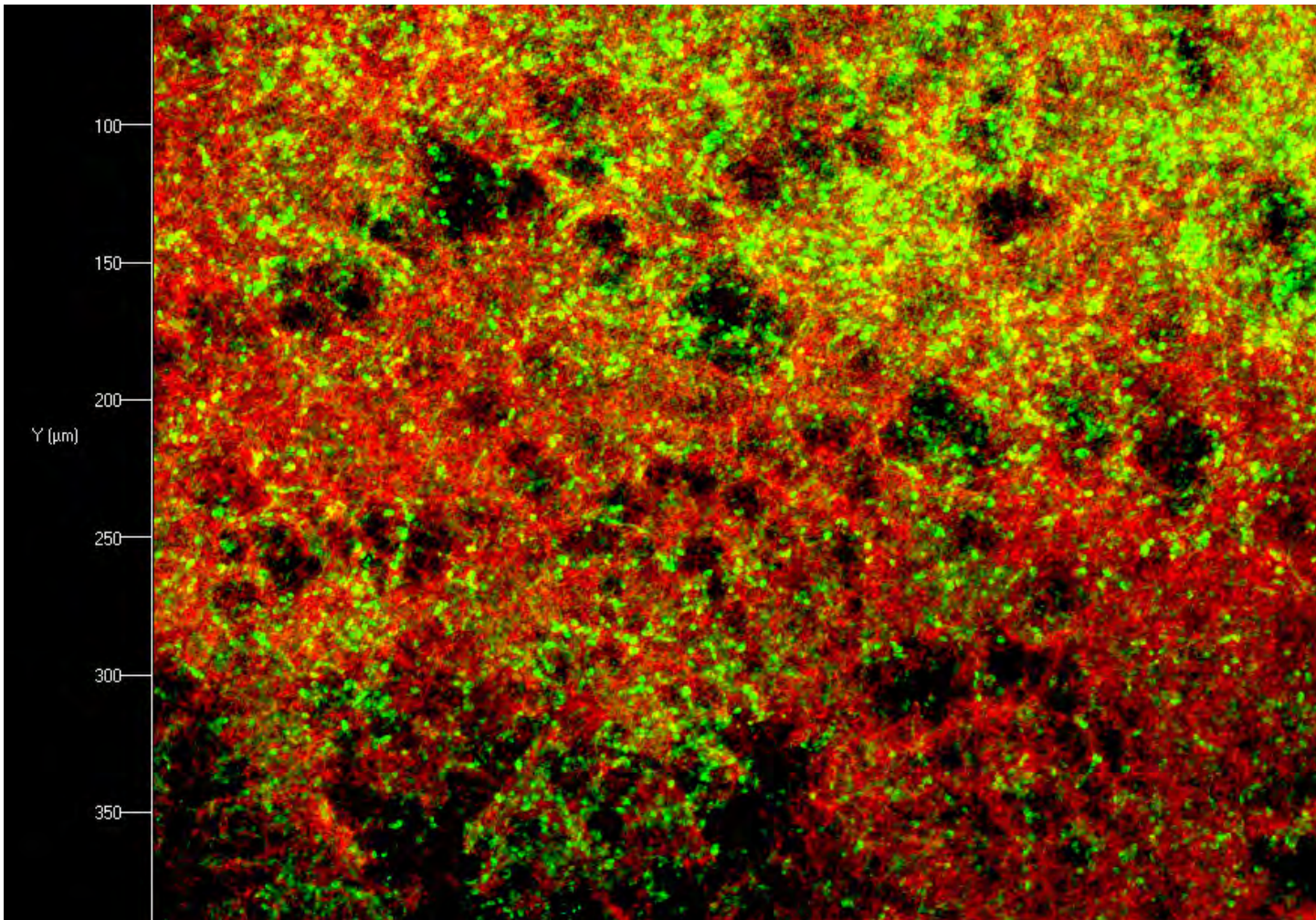
Candida albicans is the most common fungal commensal of humans and frequently associated with mucosal surfaces. Under certain circumstances the fungus can switch from a commensal to a pathogenic state causing a range of infections – from mild mucosal infections to life-threatening systemic infections. Clearly, the tight association with humans, both as a commensal and a pathogen, must have driven the evolution of mechanisms that permit rapid metabolic adaptations to the changing environments within the host, where the availability of nutrients is often limited. We follow the hypothesis that *C. albicans* has not only acquired a remarkable repertoire of metabolic adaptations to cope with the restricted nutrient supply in the diverse commensal and pathogenic niches, but also that these metabolic adaptations permit resistance to host-imposed stress, which is required for the ability of the fungus to cause disease. In addition, we postulate that metabolic adaptations which are unique to *C. albicans* are directly linked to the expression of virulence factors. For example, utilization of amino acids, an abundant source of nitrogen and carbon in the human host, increases the expression of virulence factors and aids in immunomodulation. The review by Garbe and Vylkova (*Curr Clin Micro Rpt* 2019) summarizes these findings. Thus, our long-term goal is to define the mechanistic links that connect metabolic adaptations and alterations of the commensal-to-pathogen shift to *C. albicans* pathogenicity.

Our current research includes the use of patient gut samples, an *ex vivo* blood model (with our collaboration partners), and the use of our own *in vitro* and *ex vivo* models mimicking fungal-macrophage interactions, biofilm formation, and burn wound infections. The latter models are both unique to our group and complement the portfolio of other research groups within the Leibniz-HKI. Another unique feature is our comprehensive bottom-up approach to study the role of metabolism in commensalism and virulence, starting from the effect of sensing of environmental cues on gene expression and their implication on posttranslational modifications and metabolic changes, and their role in commensalism and virulence. The use of a combination of "omics" approaches in other areas of infection biology research has made a rapid and impactful progress on understanding host-pathogen interactions. As we pointed out in our review article (*PLOS Pathogens* 2020), the methods to study metabolic changes on a global level have scarcely been used in human pathogenic fungi. One of these novel approaches is the combination of metabolic modeling and experimental validation, as used by the SBI group (Gianni Panagiotou) in collaboration with us (*ISME J* 2020).

In *C. albicans,* amino acid (AA) sensing and metabolism is interconnected with virulence networks. In this context, we study the role of Stp2, a fungal-specific transcriptional regulator of amino acid uptake, in *C. albicans* metabolism and AA utilization in particular. Together with the ASB group (Marc Thilo Figge) and the MI group (Ilse Jacobsen) we showed that strains lacking *STP2* have early defect in biofilm formation due to poor adherence and delay in hyphal growth, but

eventually form a normal biofilm with prolonged longevity (*Front Microbiol* 2020). The transcription factor Ahr1, needed for proper arginine metabolism, regulates the expression of virulence-associated genes, such as the candidalysin-expressing gene ECE1. We contributed to the work of the FS group (Oliver Kurzai) in Ruben *et al*. (*mBio* 2020). The burn wound is a highly susceptible site for opportunistic colonization and infection by bacteria and fungi. Since the burned site is enriched in fatty acids and AA, we established burn wound models of candidiasis in order to determine host and fungal responses following thermal damage. In a burn wound model using *ex vivo* human burn skin explants, we demonstrated recruitment of neutrophils towards the burn and active healing of the skin, which remained largely unaffected during *C. albicans* infection (*Sci Rep* 2020). To investigate how clinical *C. albicans* isolates from different host niches adapt to niche-specific nutrients, such as the nutrient poor macrophage phagosomes, a comparative study with multiple *C. albicans* isolates was performed. Our data reveal a high heterogeneity among vaginal isolates in interaction with the immune cells, but a relatively uniform response to *in vitro* conditions (*mSphere* 2020). In a translational study in collaboration with Dr. Bloos (University Hospital Jena) we in-

Figure: Role of metabolism in *Candida albicans* pathogenesis. *Candida albicans* metabolism plays an important role for survival of the fungus in the host and for pathogenicity. Utilization of host-derived nutrients, such as amino acids, leads to hyphal morphogenesis, a potent virulence factor in *C. albicans*. The fungus alone or in association with other pathogens can cause infections in the form of biofilm, such as within burn/severe wounds and on catheters. Currently, we are evaluating the metabolic profiles of growing biofilms, establishing a burn wound model of candidiasis using 3D tissue and examining metabolic interactions with accompanying infectious species. (Confocal image of a *C. albicans* biofilm; green: live cells, red: dead cells.)



vestigated the role of host proteins on the formation of biofilms on central venous catheters. During the course of this study, which is funded by the Center for Sepsis Control & Care (CSCC), we discovered a unique case of catheter-associated bloodstream infection caused by opportunistic bacterial pathogen *Enterobacter ludwigii* (*Infection* 2020).

Future projects will focus on expanding our understanding of the role of metabolism on fungal pathogenicity, such as in the context of mixed species biofilms both *in vitro* and *in vivo* (i.e. burn wound infection and mixed species biofilms), or following pathogenic *Candida* spp. interaction with host immune cells (i.e. macrophages and neutrophils). We expect that the planned global metabolic profiling, paired with complementary "omics" and modeling approaches, will help to close a major gap in the field. Furthermore, we aim to continue understanding the epigenetic mechanisms of *Candida* spp. adaptation to various host niches.

Selected collaborations

D'Enfert, Christophe
Institut Pasteur, Paris, France

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

Morschhäuser, Joachim
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Norrby-Teglund, Anna
Karolinska Institute, Stockholm, Sweden

Peters, Brian
University of Tennessee Health Science Center in Memphis, TN, USA

Selected publications

1. Böttcher B, Hoffmann B, Garbe E, Weise T, Cseresnyés Z, Brandt P, Dietrich S, Driesch D, Figge MT, Vylkova S (2020) The transcription factor Stp2 is important for *Candida albicans* biofilm establishment and sustainability. *Front Microbiol* 11, 794.

2. Gerwien F, Dunker C, Brandt P, Garbe E, Jacobsen ID, Vylkova S (2020) Clinical *Candida albicans* vaginal isolates and a laboratory strain show divergent behaviors during macrophage interactions. *mSphere* 5(4), e00393-20.

3. Ruben S, Garbe E, Mogavero S, Albrecht-Eckardt D, Hellwig D, Häder A, Krüger T, Gerth K, Jacobsen ID, Elshafee O, Brunke S, Hünniger K, Kniemeyer O, Brakhage AA, Morschhäuser J, Hube B, Vylkova S, Kurzai O, Martin R (2020) Ahr1 and Tup1 contribute to the transcriptional control of virulence-associated genes in *Candida albicans*. *mBio* 11(2), e00206-20.

4. von Müller C, Bulman F, Wagner L, Rosenberger D, Marolda A, Kurzai O, Eißmann P, Jacobsen ID, Perner B, Hemmerich P, Vylkova S (2020) Active neutrophil responses counteract *Candida albicans* burn wound infection of *ex vivo* human skin explants. *Sci Rep* 10(1), 21818.

5. Wagner L, Bloos F, Vylkova S (2020) Bloodstream infection due to *Enterobacter ludwigii,* correlating with massive aggregation on the surface of a central venous catheter. *Infection* 48(6), 955-958.

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

BMBF: „Integriertes Forschungs- und Behandlungszentrum Sepsis und Sepsisfolgen“ (Center for Sepsis Control & Care, kurz CSCC): Investigating the contribution of bacteria and host proteins to the development of central venous catheter-associated *Candida albicans* biofilms - CanCVC

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

Associated Group

INFECTIONS IN HEMATOLOGY / ONCOLOGY

INFECTIONS IN HEMATOLOGY / ONCOLOGY

Mission

The research 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.

Most important results

The group IHO focusses on infections in haematology and oncology and conducts both clinical research and laboratory research. It is also very active in the development of guidelines within national (Infectious Disease Working Party of the German Society for Haematology and Medical Oncology, AGIHO) and international (European Conference on Infections in Leukemia, ECIL) groups. In addition to developing guidelines the IHO strives to increase the evidence for recommendations by using the national network to conduct surveys. The election of the group leader as vice chair of the AGIHO in 2019 reflects the success of these efforts and increases the sustainability of the established network for further research. The laboratory research on the other hand is more locally embedded with strong collaborations within the Leibniz-HKI (NRZMyk, MAM, JMRC, ASB, MI) as well as the University Hospital Jena (Junior Group INSPIRE from the Institut für Biochemie, Klinik für Innere Medizin II and the Institut für Med. Mikrobiologie) and local biotechnology firms via the research Campus InfectoGnostics.

Selected Results 2018-2019

Our group focuses on immunological and clinical aspects of infections in immunocompromised hosts with a strong research interest in mould infections.

MAIT cells are rapidly activated by mould species: Mucosal associated invariant T (MAIT) cells are innate-like T cells, which have been shown to be activated by bacteria, viruses and yeasts. Our group was the first to demonstrate a rapid activation by mould-species via recognition of riboflavin as a pathogen-metabolite on MR1 of the antigen-presenting cell by the T-cell receptor of the MAIT cell (figure 1, *Eur J Immunol* 2018 and *Meth Mol Biol* 2020). Based on these results, we are currently investigating the characteristics of MAIT cells in immunosuppressed patients and are striving to find a way to determine the antifungal potential of MAIT cells since common viability tests or plating assays have not worked well in our hands.

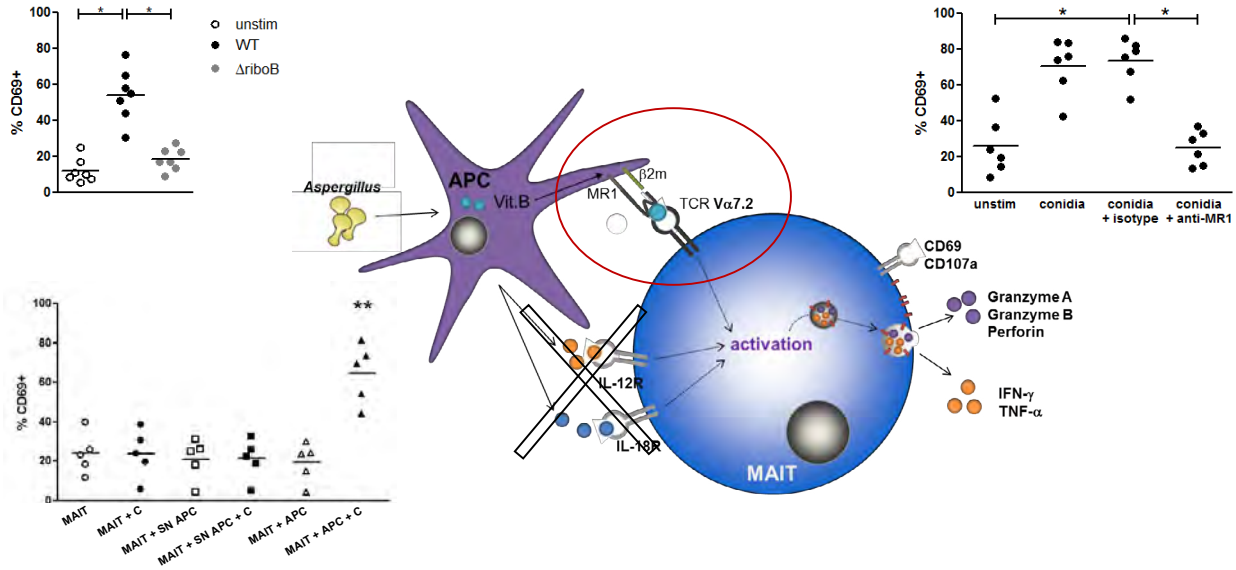
Interaction of the innate immune system with mould species: To analyse the interaction between mould species and the innate immune system, in particular phagocytes, we developed an assay to determine the phagocytotic activity of monocytes and neutrophils using flow-cytometry (*Cytometry A* 2019 and *J Vis Exp* 2019). This assay can be used to determine the activity of phagocytes from different donors and the interaction with different mould species but it is unfit to analyse the actual antifungal activity of immune cells. Also, it is inherently artificial since it uses a cell-suspension whereas invasive mould infections occur in respiratory tissue. We therefore established an infection model based on a microfluidic lung-on-chip with an air-liquid interface. Bioinformatic analysis allows us to quantify fungal growth and thus investigate infection biology of different mould species as well as antifungal activity of various immune cells from different donors. A particularly fruitful col-

laboration with INSPIRE, University hospital Jena, and ASB, Leibniz-HKI, facilitated this research.

Community-acquired respiratory viruses (CARV) including SARS-CoV-2: Another focus in clinical research has always been CARV in cancer patients. With the event of the SARS-CoV-2 pandemic, involvement in national and international guideline panels began immediately and we published the first evidence-based guideline on management of SARS-CoV-2 infection in cancer patients in autumn 2020 (*Eur J Cancer* 2020). In parallel, we published our data on the relevance of CARV in stem cell transplant recipients compared to healthy people (*Transpl Infect Dis* 2020) and could fortunately start the OncoReVir registry with funding from the Deutsche Krebshilfe. This is a registry on CARV in cancer patients comprising 9 university hospitals and is expected to recruit at least until 2022.

Perspective

Using "aspergillosis-on-chip" we hope to be able to unravel the key players in the defense of invasive mould infections in immunosuppressed patients. This includes the antifungal activity of MAIT cells as well as the effect of neutropenia and certain drugs on the susceptibility towards invasive mould infections. Also, bioinformatic analysis of the model (for example automatic quantification of fungal growth and live cell imaging) will be optimized. In addition, in cooperation with the NRZMyk the infection model will play a key role in investigating infections with drug-resistant *Aspergillus* spp.; funding for this project is granted by the IZKF Jena. Last but not least we hope to develop the infection model further into a platform for improved susceptibility testing which can ultimately be commercialized. Another ongoing



MAIT: mucosal associated invariant T cells, APC: Antigen presenting cell, C: conidia, SN: supernatant

Figure: Human MAIT cells are rapidly activated by *Aspergillus* spp. in an antigen presenting cell-dependent manner via MR1: (*Eur J Immunol* 2018).

project is to analyse the clinical relevance of drug-resistant *Aspergillus* spp. which have been increasingly reported in Europe. To date it is not clear, whether drug-resistant aspergilli are an imminent threat in Europe or whether they only play a minor role. The IZKF-funded clinician scientist will use the clinical isolates collected in the NRZMyk to shed some light on this question.

Selected collaborations

Giesen, Nicola
University Hospital Heidelberg, Germany

Hirsch, Hans H.
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Mosig, Alexander
University Hospital Jena, Germany

Teschner, Daniel
University Hospital Mainz, Germany

Lehrnbecher, Thomas
University of Frankfurt, Germany

Selected publications

1. Hartung S, Rauh C, Boettcher S, Hoang MTN, Jahreis S, Rummler S, Hochhaus A, von Lilienfeld-Toal M (2019) Measuring phagocytosis of *Aspergillus fumigatus* conidia by human leukocytes using flow cytometry. *J Vis Exp* 154.

2. Hartung S, Rauh C, Hoang TNM, Jahreis S, Wagner K, Macheleidt J, Brakhage AA, Rummler S, Hochhaus A, von Lilienfeld-Toal M (2019) Fast and quantitative evaluation of human leukocyte interaction with *Aspergillus fumigatus* conidia by flow cytometry. *Cytometry A* 95(3), 332-338.

3. Jahreis S, Boettcher S, von Lilienfeld-Toal M (2019) MAIT cell activation by fungal pathogens. *Methods Mol Biol* 2098, 167-177.

4. Rachow T, Lamik T, Kalkreuth J, Kurze S, Wagner K, Stier P, Hammersen FJ, Rüthrich MM, Winkelmann N, Klink A, Hilgendorf I, Hermann B, Lang S, Hochhaus A, von Lilienfeld-Toal M (2020) Detection of community-acquired respiratory viruses in allogeneic stem-cell transplant recipients and controls-A prospective cohort study. *Transpl Infect Dis* 22(6), e13415.

5. Giesen N, Sprute R, Rüthrich M, Khodamoradi Y, Mellinghoff SC, Beutel G, Lueck C, Koldehoff M, Hentrich M, Sandherr M, von Bergwelt-Baildon M, Wolf HH, Hirsch HH, Wörmann B, Cornely OA, Köhler P, Schalk E, von Lilienfeld-Toal M (2020). Evidence-based management of COVID-19 in cancer patients: Guideline by the Infectious Diseases Working Party (AGIHO) of the German Society for Haematology and Medical Oncology (DGHO). *Eur J Cancer* Nov;140:86-104

Major third party funding

BMBF: InfectoGnostics Research Campus – Patientenkohorte

Deutsche Krebshilfe: OncoReVir Registry

Associated Group

PHARMACEUTICAL MICROBIOLOGY

Associated Groups

PHARMACEUTICAL MICROBIOLOGY

Mission

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.

Most important results

The associated group Pharmaceutical Microbiology is affiliated both with the FSU Jena/Institute of Pharmacy and the Leibniz-HKI. Work in our group is focused on fungal natural products as potential new pharmaceuticals or as chemical signals in microbial communication. We elucidate the biochemical and genetic basis of their biosyntheses, and apply this knowledge for biotechnological compound production.

Indole alkaloids - Psilocybin is the major natural product of the psychotropic *Psilocybe* mushrooms. This compound is investigated against therapy-refractory depression in clinical phase II trials and has received "breakthrough status" by the FDA. Work on the biocatalytic production of psilocybin was continued and includes i) *in vitro* production from 4-hydroxyindole and L-serine, ii) *in vivo* production in *Aspergillus*, iii) biocatalytic production of structural congeners, and iv) research at the primary/secondary metabolism interface, which led to identification of the *S*-Adenosyl-L-methionine regeneration cycle as an important factor for high product titers.

For decades, the psilocybin-based blueing reaction of *Psilocybe* species has been an unsolved problem in natural product chemistry. In ILRS-supported work, the reaction leading to blue psilocyl oligomer formation was elucidated and a potential ecological role for the oligomer was proposed. The publication reporting these results attracted much attention and media coverage. *Psilocybe* species were also shown to produce β-carbolines, i.e. monoamine oxidase inhibitors, which may act synergistically with psilocybin.

Progress on the indole alkaloid project was made in close internal cooperation with the BMC, BT, BMN, MAM, SMB, and TTA groups and, externally, with i) the Usona Institute in Madison, WI, a non-profit foundation promoting clinical trials for depression research, and ii) the Medical University Innsbruck.

Pulvinic acids - The model basidiomycete *Serpula lacrymans* (house eater mushroom) responds to the presence of microbial consortia by producing pulvinic acid-type pigments. As an integral CRC ChemBioSys project, work aims at identifying the triggers of this reaction, likely a protease and/or a cellulase, secreted by the surrounding microbes, that damage the fungal cell wall.

Sesquiterpene aryl esters - Research on honey mushroom (*Armillaria mellea*) sesquiterpene aryl esters, the melleolides, 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. Through very intensive cooperation with Oliver Werz (FSU Jena), also within the CRC ChemBioSys, melleolides were found to prevent interaction of 5-lipoxygenase with its helper protein FLAP via selective binding to Cys159 in 5-LO, thus suppressing production of pro-inflammatory leukotrienes. The fungal translation elongation factor 2 was identified as molecular target that mediates the antifungal activity of $\Delta^{2,4}$-unsaturated melleolides.

Mortierella natural products - The "zygomycetes" have traditionally been considered poor producers of secondary metabolites. Challenging this paradigm, independent work by Markus Gressler in the PM group identified the zygomycete *Mortierella alpina* as a prolific producer of numerous natural products. Evidence is based on genomic, biochemical, and analytic data. The compounds include nonribosomally made linear and cyclic peptides, among them the malpinins which possess an exceptionally strong surfactant activity.

Perspective - Future work within the CRC ChemBioSys and EXC Microverse consortia will address signal transduction and regulation underlying natural product biosyntheses in basidiomycetes, i.e., an entirely unexplored research area. Further work focuses on regio- and stereoselective oligocyclic bioactive mushroom polyketide biosynthesis and on tryptamine-derived mushroom alkaloids.

Figure: Psilocybe cubensis.

Selected collaborations

Asiegbu, Fred
University of Helsinki, Finland

Chadeayne, Andrew
CaaMTech, Issaquah, WA, USA

Kargbo, Robert
Usona Institute, San Luis Obispo, CA, USA

Rupp, Bernhard
Medical University Innsbruck, Austria

Sherwood, Alexander
Usona Institute, Madison, USA

Tunlid, Anders
Lund University, Sweden

Selected publications

1. Lenz C, Wick J, Braga D, Garcia-Altares M, Lackner G, Hertweck C, Gressler M, Hoffmeister D (2020) Injury-triggered blueing reactions of *Psilocybe* "magic" mushrooms. *Angew Chem Int Ed* 59(4), 1450-1454.

2. Baccile JA, Le HH, Pfannenstiel BT, Bok JW, Gomez C, Brandenburger E, Hoffmeister D, Keller NP, Schroeder FC (2019) Diketopiperazine formation in fungi requires dedicated cyclization and thiolation domains. *Angew Chem Int Ed* 58(41), 14589-14593.

3. König S, Romp E, Krauth V, Rühl M, Dörfer M, Liening S, Hoffmann B, Häfner AK, Steinhilber D, Karas M, Garscha U, Hoffmeister D, Werz O (2019) Melleolides from honey mushroom inhibit 5-lipoxygenase via Cys159. *Cell Chem Biol* 26(1), 60-70.e4.

4. Blei F, Dörner S, Fricke J, Baldeweg F, Trottmann F, Komor AJ, Meyer F, Hertweck C, Hoffmeister D (2020) Simultaneous production of psilocybin and a cocktail of β-carboline monoamine oxidase inhibitors in 'magic' mushrooms. *Chem Eur J* 26(3), 729-734.

5. Fricke J, Kargbo R, Regestein L, Lenz C, Peschel G, Rosenbaum MA, Sherwood A, Hoffmeister D (2020) Scalable hybrid synthetic/biocatalytic route to psilocybin. *Chem Eur J* 37(26), 8281-8285.

Major third party funding

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

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

DFG: Biochemical and genetic basis of oligocyclic aromatic polyketide formation in basidiomycetes.

FACTS AND FIGURES

ORGANIZATION OF THE LEIBNIZ-HKI

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LEIBNIZ-HKI AT A GLANCE

82 Bachelor and Master theses

45 PhD Theses

425 Publications

357 Peer-Reviewed Publications

53 Editorial Board Memberships

1 Call for Appointments

86 Awards

451 Scientific Talks by Leibniz-HKI Employees

18 Scientific Colloquia at the Leibniz-HKI

18 Organisation of Scientific Meetings and Conferences

4 Patent applications

21/9[1] Networks and Collaborative Projects

20,3 Mio € Third Party Funding

438[2] Employees

1. Participation in 21, 9 of which are coordinated by Leibniz-HKI
2. 31.12.2020

PATENT APPLICATIONS

Besides original publications in peer-reviewed journals, intellectual property rights are an important performance parameter for research work at the Leibniz-HKI. Research teams from the main research fields of the Leibniz-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 2019/2020. Patents applied for by the Leibniz-HKI have led to a number of fruitful industrial cooperations and form the basis for application-oriented third-party funding projects.

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.

Wiech T, **Zipfel P**, Person F, Wulf S
C3/C5 convertase assays
EP19189415.3
Priority date 2019-07-31

Panagiotou G, **Heshiki Y**, Vazquez-Uribe R, Quainoo S, Sommer MOA, Glen Weiss G
Method for the modulation of cancer treatment based on analyzing the gut microbiome
US62/986,063
Priority date 2020-03-06

Brakhage A, **Kloß F**
Phagocytosis induced clearance of viruses
DE102020114148.3
Priority 2020-05-27

Hillmann F, Reimer C, Kufs JE, Valiante V
Method for producing olivetolic acid in an amoebozoa host species
DE102020117610.4
Priority: 2020-07-03

EXTERNAL FUNDING

Participation in Research Networks

EU:

BestTreat – Building a Gut Microbiome Engineering Toolbox for In-Situ Therapeutic Treatments for Non-alcoholic Fatty Liver Disease
(Marie-Skłodowska-Curie Innovative Training Network (ITN))
Duration: 2018-2022
Coordinator: Panagiotou, Gianni
Total funding: 758,000 €

FunHoMic – Deciphering the fungus-host-microbiota interplay to improve the management of fungal infections
(Marie-Skłodowska-Curie Innovative Training Network (ITN))
Duration: 2019-2022
PI: Hube, Bernhard; Jacobsen, Ilse
Total funding: 560,000 €

HDM-FUN - Host directed medicine in invasive fungal infection
(Horizon 2020 Research and Innovation action)
Duration: 2020-2024
PI: Brakhage, Axel; Hube, Bernhard
Total funding: 320,000 €

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: 226,000 €

Leibniz Association:

Leibniz ScienceCampus InfectoOptics: Combating infectious diseases with advanced optical methods (Leibniz ScienceCampus)
Duration: 2015-2022
PIs: Figge, Marc Thilo (spokesperson); Brakhage, Axel; Hube, Bernhard; Jacobsen, Ilse; Kurzai, Oliver
Total funding: 601,000 €

DFG:

Cluster of Excellence Balance of the Microverse
Duration: 2019-2025
PIs: Brakhage, Axel (spokesperson); Agler-Rosenbaum, Miriam; Beemelmanns, Christine; Barber, Amelia; Figge, Marc Thilo; Hillmann, Falk; Hertweck, Christian; Hube, Bernhard; Jacobsen, Ilse; Lackner, Gerald; Panagiotou, Gianni; Stallforth, Pierre
Total funding: 2,901,000 €

CRC 1127 ChemBioSys: Chemical Mediators in Complex Biosystems
(Collaborative Research Center)
Duration: 2014-2022
PIs: Hertweck, Christian (spokesperson); Beemelmanns, Christine; Brakhage, Axel; Stallforth, Pierre
Total funding: 2,591,000 €

CRC 1192 Immune-Mediated Glomerular Diseases
Duration: 2016-2023
PI: Zipfel, Peter
Total funding: 840,000 €

CRC 1278 PolyTarget - Polymer-based nanoparticle libraries for targeted anti-inflammatory strategies
PIs: Brakhage, Axel; Figge, Marc Thilo
Duration: 2017-2021
Total funding: 688,000 €

CRC/TR 124 FungiNet: Pathogenic fungi and their human host: Networks of Interaction
(Collaborative Research Center / Transregio)
Duration: 2013-2021
PIs: Brakhage, Axel (spokesperson), Figge, Marc Thilo; Hube, Bernhard; Jacobsen, Ilse; Kniemeyer, Olaf; Panagiotou, Gianni; Skerka, Christine; Voigt, Kerstin; Zipfel Peter F.
Total funding: 6,415,000 €

SPP 2170 InterZell - Novel production processes and multi-scale analysis, modelling and design of cell-cell and cell-bioreactor interactions
Project Towards pilot scale production of natural products with filamentous defined co-cultures
(Priority Program)
Duration: 2019-2022
PI: Agler-Rosenbaum, Miriam
Total funding: 226,000 €

BMBF:

AReST - Antifungal Resistance: From Surveillance to Treatment
(BMBF and Agence Nationale de la Recherche)
Duration: 2020
PIs: Brakhage, Axel; Hube, Bernhard
Total funding: 246,000 €

CORONA — 3Dsensation: 3D-gestützte automatisierte Dekontamination komplexer Oberflächen, Teilprojekt Infektionsdiagnostik
Duration: 2020-2023
PI: Brakhage, Axel
Total funding: 492,000 €

InfectControl: New antiinfection strategies – Science • Society • Economy
(Zwanzig20 – Partnerschaft für Innovation)
Duration: 2014-2020
PIs: Brakhage, Axel (spokesperson); Hertweck, Christian; Kloß, Florian; Kniemeyer, Olaf; Kurzai, Oliver
Total funding: 9,581,000 €

InfectoGnostics Research Campus
Duration: 2015-2025
PIs: Figge, Marc Thilo; Jacobsen, Ilse; Rosenbaum, Miriam
Total funding: 838,000 €

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 €

BMG/RKI:

NRZMyk: National Reference Center for Invasive Mycoses
Duration: 2014-2022
PIs: Kurzai, Oliver; von Lilienfeld-Toal, Marie; Voigt, Kerstin
Total funding: 719,000 €

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: 335,000 €

DZIF:

Innovative mikrobielle Quellen für neue Antiinfektiva
Duration: 2016-2021
PIs: Brakhage, Axel; Roth, Martin
Total funding: 331,000 €

Vorbereitung und Durchführung von Phase-I-Studien mit dem Antituberkulotikum BTZ043
Duration: 2017-2020
PI: Kloss, Florian
Total funding: 117,000 €

Leibniz Research Alliances:

Bioactive Compounds and Biotechnology

Health Technologies

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

Individual Projects

EU:

e-MICROBe - Energizing microbes with redox mediators for new bioproductions
(ERC Consolidator Grant)
Duration: 2020-2025
PI: Agler-Rosenbaum, Miriam
Total funding: 2,000,000 €

FUNBIOSIS – Mediators in plant pathogenic fungal-bacterial symbiosis
(Marie Sklodowska-Curie Actions - Individual Fellowships (IF))
Duration: 2018-2020
PI: Richter, Ingrid
Total funding: 171,000 €

MORPHEUS - Deciphering Bacteria-induced Morphogenesis and Protection in marine Eukaryotes
(ERC Starting Grant)
Duration: 2019-2024
PI: Beemelmanns, Christine
Total funding: 1,498,000 €

DFG:

AfuInf - Proteom-und Polysaccharidom-Analysen der initialen Infektionsphase von *Aspergillus fumigatus*
(Research Grant with Agence Nationale de la Recherche / The French National Research Agency)
Duration: 2017-2021
PI: Brakhage, Axel
Total funding: 329,000 €

Amöbophag – Molekulare Muster zur Erkennung und Diskriminierung von Pilzen während der Phagozytose durch räuberische Amöben
(Research Grant)
Duration: 2020-2023
PI: Hillmann, Falk
Total funding: 190,000 €

BiBimac - Biomimetische Synthese von glykosylierten Makrolactamen, die Aufklärung und Manipulation des Biosynthesewegs sowie Studien zu Struktur-Aktivitätsbeziehungen
(Research Grant with Agence Nationale de la Recherche / The French National Research Agency)
Duration: 2018-2022
PI: Beemelmanns, Christine
Total funding: 249,000 €

CanImmunAdapt - Die Anpassung von *Candida albicans* an Entzündungsmediatoren und die Konsequenz dieser Anpassung für die Immunerkennung und Pathogenese
(Emmy Noether Junior Research Group)
Duration: 2020-2023
PI: Gresnigt, Mark
Total funding: 894,000 €

Coenzym F420 - Neue Wege in der Cofaktor-Forschung: Entdeckung und Entwicklung Coenzym F420-abhängiger Bioprozesse
(Research Grant)
Duration: 2018-2021
PI: Lackner, Gerald
Total funding: 226,000 €

DEHAMA - Gerichtete Evolution von Adenylierungs-Domänen geleitet von Hydroxamat-Profilen
(Research Grant)
Duration: 2020-2023
PI: Kries, Hajo
Total funding: 217,000 €

Die Bedeutung reduktiver Enzyme zur Abwehr gegen die oxidative Inaktivierung primarer Stoffwechselwege in *Aspergillus fumigatus*
(Research Grant)
Duration: 2016-2019
PI: Hillmann, Falk
Total funding: 200,000 €

Die Faktor H-vermittelte Komplementevasion des Malariaparasiten *Plasmodium falciparum*
(Research Grant)
Duration: 2017-2020
PI: Skerka, Christine
Total funding: 215,000 €

Ece1-Peptide - Aufklärung der Rolle von *Candida albicans* Ece1-Peptiden
(Research Grant)
Duration: 2020-2023
PI: Hube, Bernhard
Total funding: 424,000 €

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

Gottfried Wilhelm Leibniz Prize
PI: Hertweck, Christian
Total funding: 3,000,000 €

Reduktion mikrobieller Adhäsion
(Research Grant)
Duration: 2016-2019
PI: Brakhage, Axel
Total funding: 208,000 €

SIGMOSA - Die Rolle des Glorin-Signalsystems in der Multizellulären Entwicklung Sozialer Amöben
(Research Grant)
Duration: 2018-2022
PI: Stallforth, Pierre
Total funding: 177,000 €

SMABI – Sekundärmetabolite in Amöben-Bakterien Interaktionen
(Research Grant)
Duration: 2017-2020
PI: Stallforth, Pierre
Total funding: 200,000 €

Leibniz Association:

A Molecular Targeting Approach to Combat Human Pathogenic Fungi
(Leibniz Competition)
Duration: 2017-2021
PI: Hertweck, Christian
Total funding: 748,000 €

BMBF:

PRoDICAN - Produktion von Cannabinoiden in Dictyostelium discoideum
(GO-bio Initial Project)
Duration: 2020-2021
PI: Hillmann, Falk
Total funding: 100,000 €

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

Researcher groups:

Howi - Mit Hochdruck zu neuen Wirkstoffen
(Researcher Groups)
Duration: 2020-2022
PI: Regestein, Lars
Total funding: 699,000 €

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

Next-GenBTZ - Entwicklung einer nächsten Generation von Antituberkulotika durch Metabolismus-geleitete Leitstruktur-Optimierung von Benzothiazinonen
(Researcher Groups)
Duration: 2018-2021
PI: Kloss, Florian
Total funding: 698,000 €

PiDOMICS – Pilzinfektionen: neue Verfahren zur Diagnose und zum Therapiemonitoring mit Hilfe von OMICS-Technologien und Bioinformatik
(Researcher Groups)
Duration 2017-2019
PI: Linde, Jörg; Schäuble, Sascha
Total funding: 699,000 €

SphinX – Sphingolipid-Inhibitoren – ein neues therapeutisches Konzept
(Researcher Groups)
Duration 2018-2021
PI: Valiante, Vito
Total funding: 699,000 €

Infrastructure:

DDP – Aufbau einer zielgerichteten Prozessierungslinie zur Auffindung und frühen Erprobung neuer antibiotischer Wirkstoffe - Drug-Development-Package
(Thuringian Directive on the Promotion of Research)
Duration: 2018-2019
PI: Kloss, Florian
Total funding: 631,000 €

Druka – Druckreaktorkaskade - Mit Hochdruck zu neuen Wirkstoffen
(Thuringian Directive on the Promotion of Research)
Duration: 2019-2021
PI: Regestein, Lars
Total funding: 500,000 €

TandemFerm
(Thuringian Directive on the Promotion of Research)
Duration: 2019-2020
PI: Regestein, Lars
Total funding: 493,000 €

InfConnect - Infektionen: Strategische Maßnahme zur Verknüpfung der wissenschaftlichen und wirtschaftlichen Strukturentwicklung und Profilbildung im Freistaat Thüringen
(Thuringian Directive on the Promotion of Research)
Duration: 2019-2021
PI: Heidel-Fischer, Hanna
Total funding: 250,000 €

LIFD - Leibniz-Infrastruktur für Forschungsdaten in Jena
(Thuringian Directive on the Promotion of Research)
Duration: 2020
PI: Koch, Peer-Joachim; Ramm, Michael
Total funding: 356,000 €

BTZ-Rep-PQ - Reproduktionstoxikologische Studien des Antituberkulosewirkstoffes BTZ-043
(Thuringian Directive on the Promotion of Research)
Duration: 2020
PI: Kloss, Florian
Total funding: 250,000 €

Other sources:

Boehringer Ingelheim Foundation

ENGINA - Engineering NRP-PKS-hybrid enzymes for production of γ-Amino acids and unique products
Duration: 2019-2020
PI: Beemelmanns, Christine
Total funding: 91,000 €

IMPA - Identification of Microbially Produced Amoebicides
Duration: 2018-2019
PI: Stallforth, Pierre
Total funding: 80,000 €

Daimler and Benz Foundation:

A Pipeline for Biosynthetic Engineering of Antibiotic Peptides
(Postdoc Fellowship)
Duration: 2016-2019
PI: Kries, Hajo
Total funding: 40,000 €

Deutscher Akademischer Austauschdienst

Graduate School Scholarship Programme
Duration: 2018-2019
PI: Zipfel, Peter
Total funding: 2 PhD fellowships

Dr. Illing-Stiftung

Bioaktive Naturstoffe in Amöben-Bakterien Interaktionen
Duration: 2016-2021
PI: Stallforth, Pierre
Total funding: 35,000 €

Greater Cedar Rapids Community Foundation

Role of FHRS in C3 glomerulopathy: Focus on FHR1 and FHR2
(Kidneeds Fund)
Duration: 2020-2021
PI: Zipfel, Peter
Total funding: 43,000 €

Wellcome Trust

Targeting a new kingdom: the nature and significanca of Type VI secretion system-mediated anti-fungal activity
Duration: 2019-2024
PIs: Hube, Bernhard; Jacobsen, Ilse
Total funding: 313,000 €

STAFF[1]

9 Professors

9 Group leaders

65 Scientific co-workers

108 Doctoral researchers

40 Bachelor and Master students

69 Non-scientific personnel

3 Trainees

52% Female employees

44% International scientific co-workers

1. Status 31.12.2020

PEER REVIEWED ARTICLES

Department Biomolecular Chemistry

Braga D, Last D, Hasan M, Guo H, Leichnitz D, **Uzum Z, Richter I**, Schalk F, Beemelmanns C, **Hertweck C**, Lackner G (2019) Metabolic pathway rerouting in *Paraburkholderia rhizoxinica* evolved long-overlooked derivatives of coenzyme F420. *ACS Chem Biol* 14(9), 2088-2094.

Bratovanov EV, Ishida K, Heinze B, Pidot SJ, Stinear TP, Hegemann JD, Marahiel MA, **Hertweck C** (2019) Genome mining and heterologous expression reveal two distinct families of lasso peptides highly conserved in endofungal bacteria. *ACS Chem Biol* 15(5), 1169-1176.

Costa JH, Wassano CI, Angolini CFF, **Scherlach K, Hertweck C**, Fill TP (2019) Antifungal potential of secondary metabolites involved in the interaction between citrus pathogens. *Sci Rep* 9(1), 18647.

Dörfer M, **Heine D**, König S, Gore S, Werz O, **Hertweck C**, Gressler M, Hoffmeister D (2019) Melleolides impact fungal translation via Elongation Factor 2. *Org Biomol Chem* 17, 4906-4916.

Dunbar KL, Dell M, Molloy EM, Kloss F, **Hertweck C** (2019) Reconstitution of iterative thioamidation in clostthioamide biosynthesis reveals a novel nonribosomal peptide backbone-tailoring strategy. *Angew Chem Int Ed* 58(37), 13014-13018.

Fischer D, Gessner G, **Fill TP**, Barnett R, Tron K, **Dornblut K**, Kloss F, Stallforth P, Hube B, Heinemann SH, **Hertweck C, Scherlach K**, Brunke S (2019) Disruption of membrane integrity by the bacteria-derived antifungal jagaricin. *Antimicrob Agents Chemother* 63(9), e00707-19.

Haensch VG, Neuwirth T, Steinmetzer J, Kloss F, Beckert R, Gräfe S, Kupfer S, **Hertweck C** (2019) Metal-free aryl cross-coupling directed by traceless linkers. *Chem Eur J* 25(70), 16068-16073.

Herisse M, **Ishida K**, Porter JL, Howden B, **Hertweck C**, Stinear TP, Pidot SJ (2019) Identification and mobilization of a cryptic antibiotic biosynthesis gene locus from a human-pathogenic Nocardia isolate. *ACS Chem Biol* 15(5), 1161-1168.

Hermenau R, Mehl JL, Ishida K, Dose B, Pidot SJ, Stinear TP, **Hertweck C** (2019) Genomics-driven discovery of NO-donating diazeniumdiolate siderophores in diverse plant-associated bacteria. *Angew Chem Int Ed* 58(37), 13024-13029.

König S, Pace S, Pein H, Heinekamp T, Kramer J, Romp E, Straßburger M, Troisi F, Proschak A, **Dworschak J, Scherlach K**, Rossi A, Sautebin L, Haeggström JZ, **Hertweck C**, Brakhage AA, Gerstmeier J, Proschak E, Werz O (2019) Gliotoxin from *Aspergillus fumigatus* abrogates leukotriene B4 formation through inhibition of leukotriene A4 hydrolase. *Cell Chem Biol* 26(4), 524-534.

Kramell AE, **García-Altares M, Pötsch M**, Kluge R, Rother A, Hause G, **Hertweck C**, Csuk R (2019) Mapping natural dyes in archeological textiles by imaging mass spectrometry. *Sci Rep* 9(1), 2331.

Niehs SP, Dose B, Scherlach K, Pidot SJ, Stinear TP, **Hertweck C** (2019) Genome mining reveals endopyrroles from a nonribosomal peptide assembly line triggered in fungal-bacterial symbiosis. *ACS Chem Biol* 14(8), 1811-1818.

Pancrace C, **Ishida K**, Briand E, Gatte Pichi D, Weiz AR, Guljamow A, Scalvenzi T, Sassoon N, **Hertweck C**, Dittmann E, Gugger M (2019) Unique biosynthetic pathway in bloom-forming cyanobacterial genus Microcystis jointly assembles cytotoxic aeruginoguanidines and microguanidines. *ACS Chem Biol* 14(1), 67-75.

Peng H, Ishida K, Hertweck C (2019) Loss of single domain function in modular assembly line alters size and shape of complex polyketide. *Angew Chem Int Ed* 58(50), 18252-18256.

Peng H, Ishida K, Sugimoto Y, Jenke-Kodama H, **Hertweck C** (2019) Emulating evolutionary processes

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REVIEWS, MONOGRAPHS, BOOK CHAPTERS

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Research Group **Microbial Immunology**

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Independent Junior Research Group Biobricks of Microbial Natural Product Syntheses

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Independent Junior Research Group **Biosynthetic Design of Natural Products**

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Independent Junior Research Group **Chemical Biology of Microbe-Host Interactions**

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Associated Group **Host-Fungal Interfaces**

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Associated Group **Pharmaceutical Microbiology**

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MEMBERSHIPS IN EDITORIAL BOARDS

Brakhage, Axel A.

- Applied Microbial Biotechnology
- Current Genetics
- eLife
- Molecular Microbiology

Brunke, Sascha

- Frontiers in Microbiology
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- Frontiers in Microbiology
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Kniemeyer, Olaf

- Archives of Microbiology
- Frontiers in Microbiology
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Kurzai, Oliver

- International Journal of Medical Microbiology
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- Frontiers in Cellular and Infection Microbiology
- Frontiers in Microbiology
- Fungal Biology

Voigt, Kerstin

- Acta Biologica Szegediensis
- Journal of Basic Microbiology
- MycoKeys

Vylkova, Slavena

- Frontiers in Microbiology

Zipfel, Peter F.

- Frontiers in Innate Immunity
- Molecular Immunology
- Pediatric Nephrology

LECTURES AT THE LEIBNIZ-HKI

2019

Little, Rory

University of Cambridge, UK
Novel ring-forming enzymes in polyether tetronate biosynthesis
16.04.2019

Chepkirui, Clara

Helmholtz Centre for Infection Research, Braunschweig, Germany
Tropical Basidiomycota: a rich source of novel bioactive secondary metabolites
30.04.2019

Pott, Richard

Leibniz University Hanover, Germany
Vermüllung der Ozeane – Mikroplastik in der Umwelt
19.08.2019

Geu-Flores, Fernando

University of Copenhagen, Denmark
Biosynthesis and translocation of toxic alkaloids in lupins
05.09.2019

Ene, Iuliana

Brown University, Rhode Island, USA
Genome evolution and phenotypic heterogeneity in a human fungal pathogen
10.09.2019

Goldman, Gustavo Henrique

Universidade de São Paulo, Brazil
The *Aspergillus fumigatus* CrzA and ZipD Transcription Factors Are Involved in Calcium Metabolism and the Caspofungin Paradoxical Effect
18.09.2019

Grün, Mathias

Jena Bioscience
Jena Bioscience: Turning scientific innovations into business
24.09.2019

Blackwell, Helen

University of Wisconsin-Madison, USA
Chemical tools to intercept and interrogate bacterial communication pathways
07.10.2019

Rochner, Barry R.

Biolog Inc., Hayward, CA, USA
New Electron Flow-Based Assays of Cell Bioenergetics and Mitochondrial Function in Human Cells and Yeast
22.10.2019

2020

Jahn, Nancy

Analytik Jena
Challenge sample preparation: Technologies and trends in nucleic acid extraction
11.02.2020

Farrer, Rhys

Imperial College London, UK
Genome evolution and epidemiology of fungal pathogens that infect humans and wildlife
18.02.2020

Brown, Alistair

Aberdeen Fungal Group, UK
Impact of fungal adaptation upon host-fungus interactions
19.02.2020

Bignell, Elaine

University of Manchester, UK
***Aspergillus fumigatus* - an accidental lung pathogen**
20.02.2020

Urban, Constantin

Umeå University, Sweden
Approaches to unravel mechanisms of pathogenesis and of immune regulation in opportunistic fungal infections
21.02.2020

Zelante, Teresa

University of Perugia, Italy
Immunity and tolerance during fungal infections
21.02.2020

Lampe, André

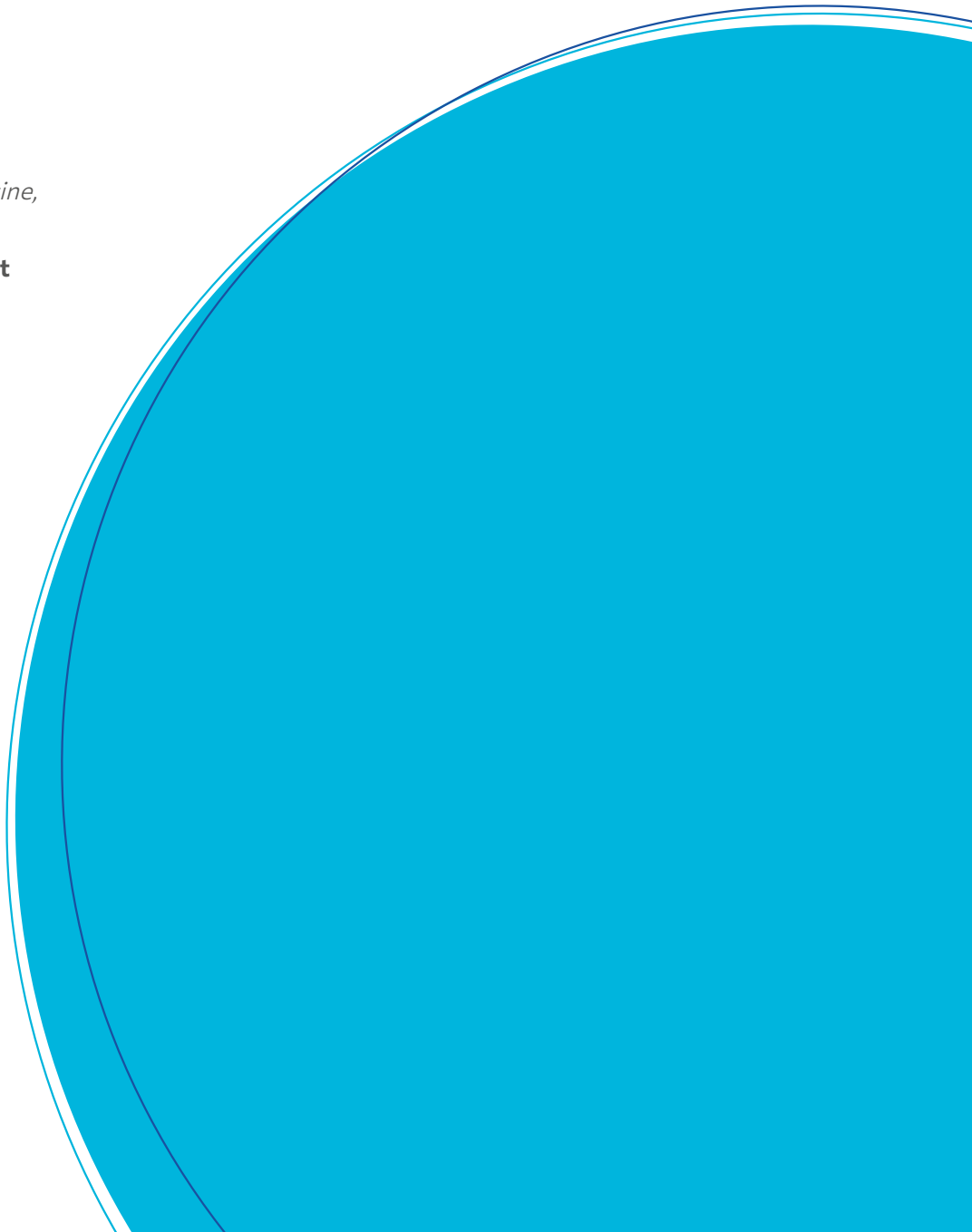
What is this SciComm thing?
10.09.2020

Wiechert, Wolfgang

Forschungszentrum Jülich GmbH, Jülich, Germany
Biotechnology from Home Office - Miniaturization, Automation, and Digitalization in Bioprocess Development
29.09.2020

Swidergall, Marc

David Geffen School of Medicine, UCLA, Los Angeles, USA
Living with a permanent guest – *Candida albicans* in the oral cavity
24.11.2020



MEETINGS, WORKSHOPS, SYMPOSIA

2019

Japanese-American-German Frontiers of Science Symposium
Beemelmanns, Christine
Kyoto, Japan

5th International Symposium on Systems Biology of Microbial Infection
Figge, Marc Thilo; Panagiotou, Gianni
Jena, Germany

Irseer Naturstofftage der DECHEMA
Hertweck, Christian
Irsee, Germany

FunHoMic Autumn School
Hube, Bernhard
Jena, Germany

Gordon Research Conference Immunology of Fungal Infections
Jacobsen, Ilse
Galveston, USA

Invasive Mycoses in Hematological Malginancies
Kurzai, Oliver
Würzburg, Germany

International VAAM Workshop: Biology of Microorganisms Producing Natural Products
Lackner, Gerald; Kries, Hajo
Jena, Germany

Training School A – Innovative Training Network "BestTreat"
Panagiotou, Gianni
Jena, Germany

Advances in Chemical Biology
Stallforth, Pierre
Frankfurt am Main, Germany

Session: Molecules of Life, Molecules in Life at the Wissenschaftsforum Aachen
Stallforth, Pierre
Aachen, Germany

VAAM Annual Meeting, special session "From Microbes to Micro-production units"
Valiante, Vito
Kaiserslautern, Germany

2. Jenaer Myelomtag
von Lilienfeld-Toal, Marie
Berlin, Germany

2020

54th Scientific Conference of the German speaking Mycological Society (DMykG) e. V. and the 3rd International Symposium of the CRC/Transregio FungiNet
Brakhage, Axel
online

Microverse I
Brakhage, Axel; Hertweck, Christian
online

FEBS Advanced Course: State-of-the-art alternative infection models to study molecular mechanisms of human fungal infections
Gresnigt, Mark; Hube, Bernhard; Jacobsen, Ilse
Jena, Germany

5th International Symposium Image-based Systems Biology
Figge, Mark Thilo
online

Irseer Naturstofftage der DECHEMA
Hertweck, Christian
Irsee, Germany

Innovative Training Network "BestTreat" Annual Meeting
Panagiotou, Gianni
online

SCIENTIFIC AWARDS

2019

Ackermann, Susanne
Beutenberg Campus Dissertation Award
Beutenberg Campus Jena e.V.

Afonso, Sara
Poster Award
11th Annual Conference of the German Society for Nephrology (DGfN)

Beemelmanns, Christine
medac Research Award
medac GmbH, Wedel

Braga, Daniel
medac Research Award
medac GmbH, Wedel

Brandt, Philipp
SIMTREA Grant
1st Summer School on High-Throughput Phenomics

Brunke, Sascha
Research Promotion Award of the DMykG
53rd German-speaking Mycological Society e.V. Conference (DMykG)

Büttner, Hannah
Exam Award of the Faculty of Biological Sciences
Friedrich Schiller University Jena

Poster Award
Association for General and Applied Microbiology e.V. (VAAM)

Cseresnyes, Zoltan
Cytometry A Best Paper 2018 Award
CYTO 2019 – 34th Congress of the International Society for Advancement of Cytometry

Cyrulies, Michael
medac Research Award
medac GmbH, Wedel

Dahse, Hans-Martin
medac Research Award
medac GmbH, Wedel

Dietrich, Stefanie
medac Research Award
medac GmbH, Wedel

Gerwien, Franziska
Poster Award
7th Conference on Physiology of Yeast and Filamentous Fungi (PYFF)

Guo, Huijuan
medac Research Award
medac GmbH, Wedel

Hänsch, Veit
Lecture Award
EYCheM Bremen

Poster Award
12th ILRS Symposium

Hasan, Mahdudul
medac Research Award
medac GmbH, Wedel

Hermenau, Ron
Leibniz Drug of the Year 2019
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Hoffmann, Bianca
Leibniz Drug of the Year 2019
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Irmscher, Sarah
Presentation Award
12th International Conference on Complement Therapeutics, Rhodos, Greece

Ishida, Keishi
medac Research Award
medac GmbH, Wedel

Kasper, Lydia
Publication Award of the DMykG Foundation
53rd German-speaking Mycological Society e.V. Conference (DMykG)

Kloß, Florian
IQ Innovation Award Central Germany
IQ Competition 2019

IQ Innovation Award Central Germany Silver in the Life Science Cluster
IQ Competition 2019

König, Annika
Publication Award of the DMykG Foundation
53rd German-speaking Mycological Society e.V. Conference (DMykG)

Kreuzenbeck, Nina
Poster Award
Association for General and Applied Microbiology e.V. (VAAM)

Kufs, Johann
Presentation Award
12th ILRS Symposium

Lackner, Gerald
medac Research Award
medac GmbH, Wedel

Last, Daniel
medac Research Award
medac GmbH, Wedel

Leichnitz, Daniel
medac Research Award
medac GmbH, Wedel

Mahler, Lisa
medac Research Award
medac GmbH, Wedel

Regestein, Lars
medac Research Award
medac GmbH, Wedel

Reimer, Christin
Poster Award
14th International Symposium on the Genetics of Industrial Microorganisms GIM2019

Richter, Ingrid
medac Research Award
medac GmbH, Wedel

Scheven, Mareike
Poster-Award
Asperfest 16 – Fungal Genetics Conference

Stallforth, Pierre
Beutenberg Campus Science Award "Life Science and Physics"
Beutenberg Campus Jena e.V.

DECHEMA Young Scientist Award for Natural Product Research
Natural Products Days Irsee

Stanisic, Aleksa
Poster Award
2nd Synthetic Biology for Natural Products Fusion Conference (BNP)

Svensson, Carl-Magnus
medac Research Award
medac GmbH, Wedel

Timme, Sandra
Best Poster Award
Systems Biology of Microbial Infection 2019

Tovar, Miguel
medac Research Award
medac GmbH, Wedel

Trottmann, Felix
medac Research Award
medac GmbH, Wedel

Voigt, Kerstin
Lecture Award
Annual Meeting of the Korean Society of Mycology

Poster-Award
Annual Meeting of the Korean Society of Mycology

2020

Allert, Stefanie
Frontiers Award
German Society for Hygiene and Microbiology e. V. (DGHM), special group Eukaryotic pathogens

Arp, Johannes
medac Research Award
medac GmbH, Wedel

Beemelmanns, Christine
Chemistry Lecturer Award
Chemical Industry Fund

Goering Visiting Professorship
Goering Visiting Professor at the University of Wisconsin, Madison, USA

medac Research Award
medac GmbH, Wedel

Student Housing Lecturer Award
University of Wisconsin, Madison, USA

Brandt, Philipp
Poster Award
54th Scientific conference of the German-speaking Mycological Society e.V.(DMyKG).,
3rd International Symposium of the CRC/Transregio FungiNet

Cseresnyes, Zoltan
medac Research Award
medac GmbH, Wedel

DGHM Paper of the month, February 2020

German Society for Hygiene and Microbiology e. V. (DGHM)

DGHM Paper of the month, November 2020
German Society for Hygiene and Microbiology e. V. (DGHM)

Cyrulies, Michael
Leibniz Drug of the year 2020
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Dahse, Hans-Martin
medac Research Award
medac GmbH, Wedel

Goldmann, Marie
Poster Award
9th Advances Against Aspergillosis and Mucormycosis, Lugano/Schweiz

medac Research Award
medac GmbH, Wedel

Götze, Sebastian
medac Research Award
medac GmbH, Wedel

Guo, Huijuan
medac Research Award
medac GmbH, Wedel

Hartung, Susann
Poster Award
54th Scientific conference of the German-speaking Mycological Society e.V.(DMyKG).,
3rd International Symposium of the CRC/Transregio FungiNet

Heinekampf, Thorsten
medac Research Award
medac GmbH, Wedel

Hertweck, Christian
Ernst Jung Award for Medicine
Jung Foundation postponed

Inhoffen Medal
Friends of the Helmholtz Centre for Infection Research postponed

Leibniz Drug of the year 2020
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Irmscher, Sarah
Doctoral Thesis Award
Faculty of Biological Sciences, Friedrich Schiller University Jena

Ishida, Keishi
Leibniz Drug of the year 2020
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Klapper, Martin
Doctoral Thesis Award
Faculty of Chemistry and Earth Sciences, Friedrich Schiller University Jena; Analytik Jena AG

Kniemeyer, Olaf
Poster Award
9th Advances Against Aspergillosis and Mucormycosis, Lugano/Schweiz

Kries, Hajo
medac Research Award
medac GmbH, Wedel

Poster Award
DECHEMA Natural Products

Kurzai, Oliver
DGHM Main Award
6th joint Meeting of the German Society for Hygiene and Microbiology e. V. (DGHM) and Association for General and Applied Microbiology e.V. (VAAM)

Lackner, Gerald
medac Research Award
medac GmbH, Wedel

Rafiq, Muhammad
medac Research Award
medac GmbH, Wedel

Regestein, Lars
Leibniz Drug of the year 2020
Leibniz Research Alliance Bioactive Compounds and Biotechnology

medac Research Award
medac GmbH, Wedel

Richter, Ingrid
Leibniz Drug of the year 2020
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Schmidt, Franziska
medac Research Award
medac GmbH, Wedel

Schmidt, Franziska
DGHM Paper of the Month, November 2020
German Society for Hygiene and Microbiology e. V. (DGHM)

Sprenger, Marcel
Publication Award
Annual meeting 2020 German-speaking Mycological Society e.V. Conference (DMykG)

Stallforth, Pierre
Academy Award Chemistry
Academy of Science Göttingen

Award of the Dr.-Otto-Röhm Memorial Foundation
Dr.-Otto-Röhm Memorial Foundation

medac Research Award
medac GmbH, Wedel

Trottmann, Felix
Leibniz Drug of the year 2020
Leibniz Research Alliance Bioactive Compounds and Biotechnology

Willing, Karsten
medac Research Award
medac GmbH, Wedel

Zhang, Shuaibing
medac Research Award
medac GmbH, Wedel

APPOINTMENTS

Zielinski, Christina
Call for a W3 Professorship in Infection Immunology at Friedrich Schiller University Jena (2020)

GRADUATIONS

2019

Allert, Stefanie
Pathogenicity mechanisms of *Candida albicans* during translocation through epithelial barriers
Friedrich Schiller University Jena

Askitosari, Theresia
Engineering *Pseudomonas putida* KT2440 for Efficient Bioelectrochemical Production of Glycolipids
RWTH Aachen University

Baldeweg, Florian
Untersuchungen zu mono-, di- und oligomeren mikrobiellen Naturstoffen aus Aminosäuren
Friedrich Schiller University Jena

Benndorf, Rene
Phylogenetic and biochemical analysis of Actinobacteria isolated from fungus-growing termites
Friedrich Schiller University Jena

Berger, Carola
Genome based investigations towards understanding carbon source dependent bioelectrochemical activity of *Pseudomonas aeruginosa* strains
RWTH Aachen University

Brandt, Philip
Polyketide aus Basidiomyceten: Untersuchungen zur Biosynthese und Rolle in der mikrobiellen Kommunikation
Friedrich Schiller University Jena

Engert-Ellenberger, Nicole
The role of oxygen on the interaction of *Candida albicans* with intestinal epithelial cells
Friedrich Schiller University Jena

Ferling, Iuliia
Influence of fungal melanins on the cell-autonomous defenses in amoebae
Friedrich Schiller University Jena

Hanf, Benjamin
Adaptation strategies of *Aspergillus* species to environmental challenges
Friedrich Schiller University Jena

Heshiki, Yoshitaro
Studying microbial communities through next generation sequencing
The University of Hong Kong (HKU)

Irmscher, Sarah
Funktion des Faktor H-verwandten Proteins 1 (FHR1) in der Inflammation
Friedrich Schiller University Jena

Klapper, Martin
Pseudomonas-derived Secondary Metabolites in Amoebae-Bacteria Interactions
Friedrich Schiller University Jena

Klaus, Maximilian
Infektionen bei Patienten mit einem Multiplen Myelom – eine retrospektive Kohortenanalyse.
Friedrich Schiller University Jena

Radosa (née Novohradská), Silvia
Molecular targets of pathogenic fungi during amoeba predation by soil amoebae
Friedrich Schiller University Jena

Rischer, Maja
Identification and Functional Analysis of Natural Products Involved in Marine Microbe - Invertebrate Interactions
Friedrich Schiller University Jena

Rudnick, Ramona
Charakterisierung von Complement Factor H Related Protein 5 (CFHR5)
Friedrich Schiller University Jena

Rüthrich, Maria
Diffus großzelliges B-Zell-Lymphom: Eine retrospektive Registerstudie am Universitätsklinikum Jena mit Subgruppenanalyse
Friedrich Schiller University Jena

Scheven, Mareike
Regulation der Eisenhomöostase in *Aspergillus fumigatus*.
Friedrich Schiller University Jena

Schlembach, Ivan
Investigations on the use of defined co-cultures for the consolidated bioprocessing of cellulose to itaconic acid
RWTH Aachen University

Schulze, Friederike
Autoimmune C3 glomerulopathy: complement inhibitors affect

complement control by autoantibodies
Friedrich Schiller University Jena

Stroe, Maria
Awakening of secondary metabolite gene clusters by microbial interaction – biosynthesis and ecological function of produced compounds
Friedrich Schiller University Jena

Thongkongkaew, Tawatchai
Genomics-Driven Discovery of Secondary Metabolites from *Burkholderia* spp. that Interact with Fungi
Friedrich Schiller University Jena

Vivas, Wolfgang
Modulation of dendritic cell function by the fungal quorum sensing molecule farnesol
Friedrich Schiller University Jena

Weber, Thomas
Development and evaluation of a process to isolate picolitre compartments of a microfluidic bioassay to search for new microbial compounds
Technische Universität Ilmenau

Wick, Jonas
Untersuchungen zu Naturstoff-Biosynthesen von Basidiomyceten der Ordnung Agaricales
Friedrich Schiller University Jena

Zheng, Tingting
A systems biology approach for studying human diseases
The University of Hong Kong

2020

Blei, Felix
Untersuchungen zur Biosynthese von Indolalkaloiden aus den Basidiomyceten der Gattung Psilocybe
Friedrich Schiller University Jena

Chen, Jiarui
Bioinformatics approaches for the comprehensive study of the microbiome
The University of Hong Kong (HKU)

Dörfer, Max
Untersuchungen zu Struktur-Aktivitätsbeziehungen und zum Wirkmechanismus der Melleolid-Antibiotika
Friedrich Schiller University Jena

Dworschak, Jan
Synthetic approaches to biosynthetic elucidation of the NRPS-derived cyclopeptides aspirochlorine, gliotoxin and jagaricin
Friedrich Schiller University Jena

Flak, Michal
Secondary metabolites in the interaction of *Aspergillus fumigatus* and *Pseudomonas aeruginosa* in cystic fibrosis sputum
Friedrich Schiller University Jena

Fricke, Janis
Genetische und biochemische Grundlage der Indolalkaloidbildung in Basidiomyceten und biotechnologische Produktion des Psilocybins
Friedrich Schiller University Jena

Goldmann (née Röcker), Marie
Molekulare Mechanismen der Interaktion von *Aspergillus fumigatus* mit dem Immunsystem
Friedrich Schiller University Jena

Gore, Sagar
Pattern recognition methods for the prediction of chemical structures of fungal secondary metabolites
Friedrich Schiller University Jena

Halder, Luke
The immediate early immune response of immune cells to *Candida albicans*
Friedrich Schiller University Jena

Hassan, Mohammed
The influence of cell surface attributes on the phagocytic vulnerability of *Lichtheimia* strains
Friedrich Schiller University Jena

Hengoju, Sundar
A droplet microfluidic system with integrated optical fibers for multi-parametric analysis of microbiological samples
Friedrich Schiller University Jena

Hoang Thi, Ngoc Mai
Establishment of "Aspergillosis on-a-chip", a novel disease model to study *Aspergillus fumigatus* infections at the air-liquid interface in the human lung alveolus
Friedrich Schiller University Jena

Kufs, Johann
Developing molecular tools for the *de novo* assembling of biosynthetic routes
Friedrich Schiller University Jena

Lackus, Natalie
The biochemistry of volatile and non-volatile specialzed metabolites in poplar
Max Planck Institute for Chemical Ecology Jena / Friedrich Schiller University Jena

Lin, Jun
Development of a user-friendly heterologous expression system and its applications for natural product biosynthesis
Friedrich Schiller University Jena

Niehs, Sarah Patricia
Genomics-Driven Discovery of Natural Products from Symbiotic *Burkhoderia* Species
Friedrich Schiller University Jena

Pawlik, Tony
The *Candida albicans* factor MNN9 modulates cytokine production in distinct epithelial cell types
Friedrich Schiller University Jena

Ruben, Sophia
Ahr1-dependent regulation of ECE1 and other core filamentation response genes in *Candida albicans*
Friedrich Schiller University Jena

Sprenger, Marcel
Survival and proliferation of human pathogenic *Candida* species within phagocytes
Friedrich Schiller University Jena

Tank, Cedric
Produktion und Funktion von Pigmenten beim Abbau von Cellulose durch obligat anaerobe Clostridien
Friedrich Schiller University Jena

BACHELOR AND MASTER THESES

Bachelor 2019

Ait Mansour, Rania
Der Effekt von FHR1 auf die Phagozytose von spätapoptotischen humanen Endothelzellen (HUVECs)
Friedrich Schiller University Jena

Alscher, Christina
Mikrobielle Produktion und Aufarbeitung von Phenazinen
University of Applied Sciences Jena

Franke, Ulrike S.
Untersuchungen zu FHR1 als terminaler Komplementregulator
Friedrich Schiller University Jena

Fuchs, Tessa
Charakterisierung des protektiven Einflusses von HIF-1α auf die Sauerstoff-abhängige *C. albicans*-Enterozyten-Interaktion
Friedrich Schiller University Jena

Griehl, Christoph
α-Enolase (Eno1) von *Candida albicans* und *Aspergillus fumigatus* bindet humane CD4+ T-Zellen und verändert die Immunantwort
Friedrich Schiller University Jena

Jochem, Seraphine
Etablierung einer anaeroben Mischkultur aus *Clostridium autoethanogenum* und *Clostridium kluyveri*
Friedrich Schiller University Jena

Kage, Franziska
Charakterisierung der Genexpression von Zellwandhydrolasen aus *Aspergillus fumigatus* unter Einfluss von Wirtszellen, Hypoxie und Bakterien
Friedrich Schiller University Jena

Katzengruber, Leon
Method development for gas analysis of fermentation processes and fatty acid biomarker analysis on a gas chromatograph
Friedrich Schiller University Jena

Köhler, Tobias
Auswirkungen der physikalischen Interaktion zwischen *Candida albicans und Enterococcus faecalis* auf die Wirtszellinvasion
Friedrich Schiller University Jena

Mendler, Robin
Identifizierung von neuen Naturstoffen aus *Enterovibrio pacificus* basierend auf *in silico* Studien
Friedrich Schiller University Jena

Meyer, Anne-Christin
Der Einfluss darmlokalisierter Metaboliten auf die Virulenz von *C. albicans*
Friedrich Schiller University Jena

Meyer, Saskia
Etablierung eines gemischten Biofilmprotokolls für *Candida albicans* und *Enterococcus faecalis*
University of Applied Sciences Jena

Otto, Janine
Strategien zur Aktivierung stiller Gencluster in insektiziden Bakterien (*Chromobacterium vaccini*)
Friedrich Schiller University Jena

Semesh, Gwladys
Candida albicans filamentation and biofilm formation during the interplay with *Proteus mirabilis*
Friedrich Schiller University Jena

Warschinke, Maria
Krankheitsassoziierte Mutanten des Faktor H-verwandten Proteins 2 binden verstärkt an nekrotische Zelloberflächen
Friedrich Schiller University Jena

Wegener, Jamila
The role of carotenoids in the interaction of Mucor circinelloides with murine alveolar macrophages
Friedrich Schiller University Jena

Zeuch, Henriette
Charakterisierung der *C. albicans* eed1Δ/Δ Mutante in Interaktion mit murinen Makrophagen und Neutrophilen und Untersuchung des Einflusses von Farnesol auf den Metabolismus des Wildtyps
Friedrich Schiller University Jena

Ziegler, Svenja
Pleiotrope und Genom-basierte Strategien zur Aktivierung stiller Biosynthese-Gencluster in *Clostridium saccharoperbutylacetonicum*
University of Applied Sciences Jena

Master 2019

Arnreich, Sindy
Filamentation-dependent interactions between *Candida albic*ans and macrophages, endothelial cells and hepatocytes
Friedrich Schiller University Jena

Böttcher, Sarah
Human MAIT cells as a new player in the immune response against filamentous fungi
Friedrich Schiller University Jena

Bulman, Fionnuala
Characterisation of host responses to *Candida albicans* in a native human burn infection model of candidiasis
Friedrich Schiller University Jena

Cao, Xueqi
Stratifying macrolide treatment in community-acquired pneumonia patients by machine learning methods - using clinical and etiological data
Friedrich Schiller University Jena

Dally, Lina, Juliane
Effect of Ece1 peptides on *C. albicans* and *C. albicans*-host cell interactions
Friedrich Schiller University Jena

Daniel, Jan-Martin
Biochemical and metabolomic studies on *Podaxis* sp.
Friedrich Schiller University Jena

Demmler, Richard
Biochemische Untersuchungen zur Regeneration des Methyldonors während der Psilocybin-Biosynthese
Friedrich Schiller University Jena

Faber, Marius
Weiterführende phylogenetische und metabolische Analysen von *Pseudoxylaria* spp
Friedrich Schiller University Jena

Gude, Finn
Investigation of polythioamide biosynthesis in anaerobic bacteria
Friedrich Schiller University Jena

Hasan, Md Zahidul
Response of human endothelial cells to *Candida albicans* induced TGF-b1-transporting cell vesicles
Friedrich Schiller University Jena

Hitzler, Sophia
Investigation of biosynthetic gene clusters by heterologous expression studies
Friedrich Schiller University Jena

Hüsken, Annika
Repairing the subdomain swapped NRPS sdVGrsA
Friedrich Schiller University Jena

Kalthoff, Elias
Enzymatic and chemical crosslinking in the rhizoxin assembly line
Friedrich Schiller University Jena

Kaune, Ann-Kristin
The role of host albumin during Infection of vaginal epithelial cells with *C. glabrata*
Friedrich Schiller University Jena

Kröber, Tabea
Development and optimization of enzymatic regeneration systems for coenzyme F420
Friedrich Schiller University Jena

Kröller, Sarah
Candida albicans Tef1 binds to Toll-like receptor 4 and induces an inflammatory cytokine response of human dendritic cells
Friedrich Schiller University Jena

Kyoyoung, Seo
Optimization of the fermentation process for production of the antibiotic jagaricin
Friedrich Schiller University Jena

Mahmudul, Hasan
Substrate specificity of key enzymes involved in the biosynthesis of coenzyme 3PG-F420
Friedrich Schiller University Jena

Okoli, Eberechukwu, Maryann
Candida albicans amino acid perpeases-packaging chaperone Csh3 is important for early stages of biofilm formation
Friedrich Schiller University Jena

Paschold, André
Synthesis of *Pseudomonas*-derived secondary metabolites and analogs
Friedrich Schiller University Jena

Schlabach, Kevin
Studies towards the biosynthesis of *Pseudomonas* – derived secondary metabolites
Friedrich Schiller University Jena

Schmalzl, Anica
Polyol-Makrolid-produzierende Streptomyzeten und deren Rolle in *Chlamydomonas* sp./*Aspergillus* sp. Gemeinschaften
Friedrich Schiller University Jena

Sprague, Jacob
Molecular analysis of recognition patterns of pathogenic fungi during amoeba predation
Friedrich Schiller University Jena

Telle, Carl
Veterinärarzneimittel in Wirschaftsdüngern – Entwicklung einer angepassten Analytik und Untersuchung von Wirkstoffreduktion
Friedrich Schiller University Jena

Wagner, Julian
Nutzung einer natürlichen Antikörperbibliothek zur Selektion und Expression von Hühnerantikörpern
University of Applied Sciences Jena

Wagner, Justine Alexandra
Pathogen-spezifische Effekte bei Immundysregulationen im Blut von CGD-Patienten unter Anwendung pharmakologischer Modulation in gesundem humanem Vollblut
University of Applied Sciences Jena

Bachelor 2020

Ahlheit, Daniel
Pinpointing residues that modulate substrate specificity in condensation domains
Friedrich Schiller University Jena

Besser, Sophie
Der Einfluss humanpathogener Erreger auf den Metabolismus und die Struktur von *C. albicans* Biofilmen.
Friedrich Schiller University Jena

Fließ, Jonas
Streptomyces-derived modulators of multicellular development
Friedrich Schiller University Jena

Hermann, Kim
Herstellung und Testung einer Affinitätssäule zur Isolierung von Coenzyme-F420-abhängigen Enzymen
Coburg University of Applied Sciences and Arts

Himmel, Maximilian
Bakterielle Hämolysinexpression und enterozytäre Zytokinproduktion während *Proteus mirabilis* – Candida albicans Koinfektion
Friedrich Schiller University Jena

Ivanov, Lia
Role of FHR1 as a complement regulator
Friedrich Schiller University Jena

Jeß, Sebastian Jan-Philip
Untersuchung zur Ammoniak-abhängigen Hemmung des Wachstumsvon *Aspergillus fumigatus* durch *Dicytostelium discoideum*
Friedrich Schiller University Jena

Merseburger, Peter
Produktion von nichtribosomalen Peptiden in Zygomyceten des *Mortierella alpina*-Komplexes
Friedrich Schiller University Jena

Motter, Jonas
Untersuchungen zum Polyketidstoffwechsel in *Cortinarius*-Arten
Friedrich Schiller University Jena

Peil, Teresa
Construction of a multi-gene expression vector for the production of Gramicidin S in the social amoeba *Dictyostelium discoideum*
Friedrich Schiller University Jena

Porschitz, Pauline
Effect of AAT and other human serum proteins on *C. albicans* pathogenicity strategies
Friedrich Schiller University Jena

Preißler, Miriam
Exploring the promiscuity of the autoinducer peptide biosynthetic machinery of *Ruminiclostridium cellulolyticum*
Friedrich Schiller University Jena

Rost, Nathalie
Charakterisierung von murinen Faktor H verwandten Proteinen
Friedrich Schiller University Jena

Master 2020

Austermeier, Sophie
The influence of human serum albumin on *Candida albicans'* pathogenicity mechanisms
Friedrich Schiller University Jena

Bauer, Johanna
Biosynthese von Cyclopropanol-substituierten Naturstoffen in Bakterien
Friedrich Schiller University Jena

Buchheim, Stefanie
Development of enzymatic assays in picolitre droplets enhanced through fluorescence encoding
Friedrich Schiller University Jena

Chandrasekar, Prashant
Testing the working range of the Mitos Dropix device for subsequent picoliter droplet generation
University of Applied Sciences Jena

Cheong, YiEnn
Metabolic engineering of the filamentous fungus *Blakeslea trispora*
Friedrich Schiller University Jena

Ellerhorst, Mark
Metabolomics-based investigation of the biosynthesis and biological role of the redox cofactor mycofactocin in *Saccharopolyspora erythraea*
Friedrich Schiller University Jena

Espino, Martínez, Jordi
Characterization of jagaricin formation in lab-scale cultivation
Friedrich Schiller University Jena

Herböck, Barbara
Produktion von Polyketiden in *Escherichia coli* mit Hilfe eines pMGE-Multiexpressionssystems
Friedrich Schiller University Jena

Kindel, Till
Development of antifungal prodrugs
University of Applied Sciences Jena

Lapierre, Thibault
Methodology and synthetic considerations focused on the A-ring of an-titubercular nitrobenzothiazinones and evaluation of the impact on in vitro hydride-Meisenheimer complex formation
Ecole Nationale Supérieure de Chimie de Montpellier

Maaz, Baig
Development and scale-up of an upstream and down-stream process for the riboflavin alike chromophore Fo.
Friedrich Schiller University Jena

Mansouri, G., Elham
Involvement of receptors in vesicle release by monocytes in response to *C. albicans*
Friedrich Schiller University Jena

Matthies, Nina
Expression patterns in the reductive pathway of iron acquisition in *Lichtheimia corymbifera*
Friedrich Schiller University Jena

Merodio, Matteo
Characterization of a redox co-factor to facilitate microbial electron uptake and utilization from a cathode
Friedrich Schiller University Jena

Neumann, Adrian
Untersuchung zur Methyltransferase-Reaktion in der Biosynthese von Basidiomyceten-Naturstoffen
Friedrich Schiller University Jena

Özbay, Furkan
Cloning of an hexanol production pathways for further applications
Friedrich Schiller University Jena

Palme, Diana
Characterization of *Candida albicans* induced microRNA in human cell
Friedrich Schiller University Jena

Pieper, Franziska
The role of the putative vacuole transporter Ctr2 of *Candida glabrata* under copper stress and during interaction with macrophages
Friedrich Schiller University Jena

Saeed, Naumann
The role of the peroxiredoxin Aspf3 during oxidative stress and iron limitation in *Aspergillus fumigatus*
Friedrich Schiller University Jena

Saghir, Zubaish
Utilization of phenazines pyocyanin and phenazine-1-carboxylic acid by *Enterobacter aerogenes*
Friedrich Schiller University Jena

Schuck, Noreen
Charakterisierung der Zelltoxizität des Antimykotikums Jagaricin in Zellkultur und in einem mikro-fluidischen Biochip-Modell der invasiven pulmonalen Aspergillose
Friedrich Schiller University Jena

Schweer, Elena
In vitro efficacy studies of sterile fecal microbiome transplant towards *Clostridioides* spp. Infection
Friedrich Schiller University Jena

Seibold, Paula
Genetische und biochemische Untersuchung der Laetiporsäure-Biosynthese
Friedrich Schiller University Jena

Unger, Sandra
Biosynthese von Cyclopropanol-substituierten Naturstoffen in Bakterien
Friedrich Schiller University Jena

Wasmuth, Ina
Etablierung eines fluoreszenzbasierten Assays für nichtribosomale Peptidsynthetasen
Friedrich Schiller University Jena

IMPRESSUM

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– Hans Knöll Institute –

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