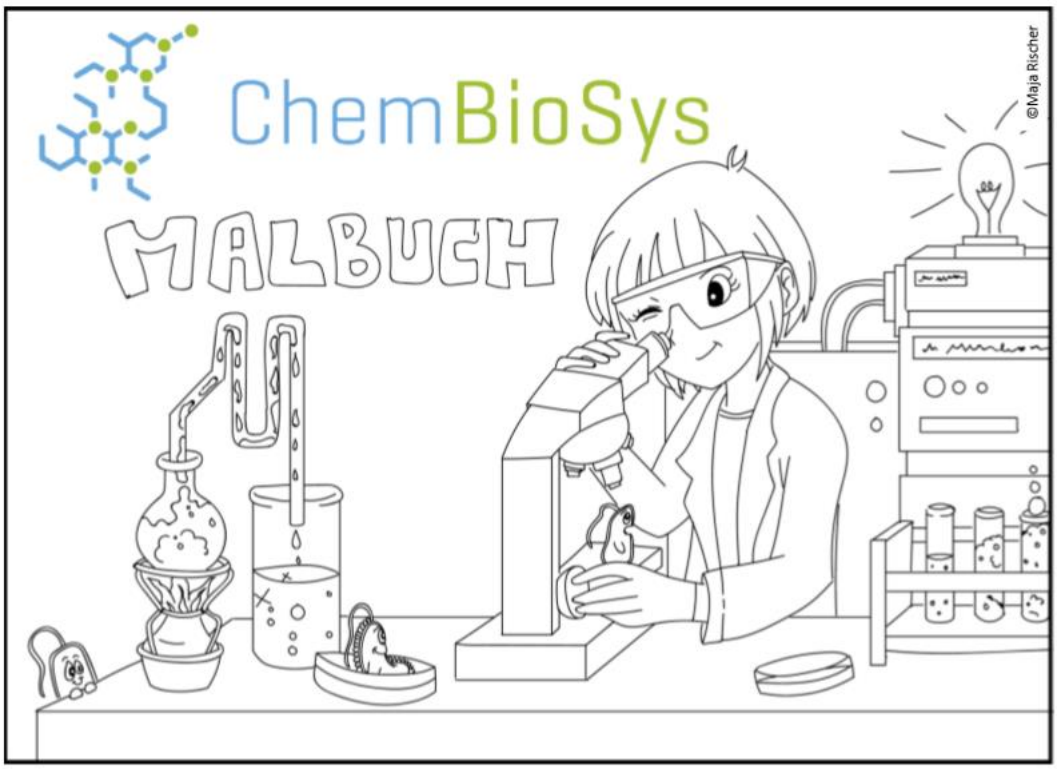
Institut für Mikrobiologie

FRIEDRICH-SCHILLER-
UNIVERSITÄT
JENA

Jahresbericht 2019



Vorwort

Liebe Leserin, lieber Leser,

im letzten Jahr hat das Institut mit der Ankunft der beiden neuen Mikrobiologen einen großen Schritt gemacht. Kai Papenfort (Lehrstuhl für Allgemeine Mikrobiologie) und Christian Jogler (Lehrstuhl für Mikrobielle Interaktionen) werden zunehmend an der neuen Gestaltung der Forschung und Lehre beteiligt sein. Die Vorstellung ihrer jeweiligen Arbeiten bereichert diesen Jahresbericht. Herzlich willkommen!

Genauso herzlich willkommen sind uns die neuen Mitglieder des Instituts aus dem Leibniz-Institut für Naturstoffforschung Hans-Knöll-Institut, Thilo Figge, und dem Forschungsinstitut für gartenbauliche Kulturpflanzen, Philipp Franken. Beide sind ebenfalls in die Lehre im Masterstudiengang Microbiology involviert, so dass wir eine große Bandbreite von Forschungsprojekten auch in den Studiengängen präsentieren können.

Die neuen Forschungsrichtungen werden auch die von der Carl-Zeiss-Stiftung weiterhin geförderte Graduiertenschule „Jena School for Microbial Communication“ bereichern. Im Rahmen der langen Nacht der Wissenschaften konnte der Sonderforschungsbereich „ChemBioSys“ ein Malbuch vorstellen, dass die Projekte für ein junges Publikum verständlich darstellt. Diese schöne Outreach-Aktivität zeigt, dass sich Wissenschaft mit ihrer öffentlichen Förderung sehr wohl auch einem breiten Publikum zeigen kann.

Die Unterbringung der neuen Professoren und auch der neuen Professuren im Rahmen des Exzellenzclusters „Balance oft he Microverse“ werden eine große Herausforderung darstellen. Der notwendige Umbau der Neugasse 24 hat sich leider weiter verzögert, eigentlich sollte es bereits in 2019 fertiggestellt sein. Wir hoffen sehr, dass es in 2020 bezugsfertig wird.

Jena, im Februar 2020

Institut für Mikrobiologie
Fakultät für Biowissenschaften
Friedrich-Schiller-Universität

Lehrstuhl für Mikrobielle Kommunikation

Prof. Dr. Erika Kothe

1. Forschung

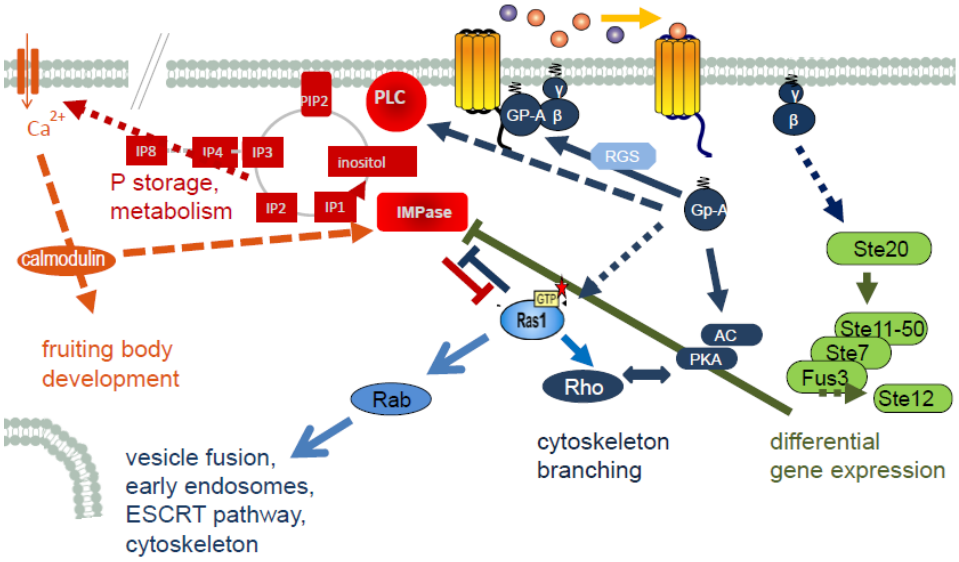
„Omics“ des höheren Basidiomyceten *Schizophyllum commune*

Befall mit *Schizophyllum commune* an einem Straßenbaum vor den Rosensälen, Fürstengraben Jena

Die Ausbreitung des weltweit verbreiteten Weißfäulepilzes *Schizophyllum commune,* der sogar auf dem Gelände der Universität natürlicher Weise vorkommt, ist eng an die sexuelle Vermehrung gekoppelt. Die Gene der Kreuzungstyploci, die einerseits für Transkriptionsfaktoren, andererseits für Pheromone und G-Protein-gekoppelte 7-Transmembrandomänen-Rezeptoren kodieren, sind durch verschiedene intrazelluläre Signaltransduktionsketten mit den phänotypischen Ausprägungen verbunden.

Von Interesse sind die Rezeptoren, die zwischen mindestens 20 verschiedenen Liganden unterscheiden können und so zu mehr als 20.000 „Geschlechtern“ oder Spezifitäten des Pilzes in der Natur beitragen. Die hohe Zahl unterschiedlicher Liganden können erkannt werden, weil zusätzlich vorkommende, ähnliche Rezeptoren (B-like receptors, Brl’s), die allein keine Signaltransduktion einleiten, die Erkennung unterstützen. Ein Gen *thn*, ein Mitglied der Familie von Regulatoren (*regulator of G-protein signaling*), das häufig in Mutanten durch ein Transposon ausgeschaltet wird, zeigte eine Störung der Signaltransduktion durch das Pheromonrezeptorgen *bbr2*. Neben einem veränderten Wachstum und Kreuzungsverhalten konnte bei solchen Mutante auch eine Veränderung des Volatiloms gefunden werden (Dissertation Sophia Wirth, 2019). Die Biosynthese von Sesquiterpenen wurde in einer Masterarbeit studiert (Masterarbeit Rabia Korkmaz, 2019).

Als Antwort auf die Erkennung des Pheromons eines geeigneten Kreuzungspartners wird intrazellulär durch ein heterotrimeres G-Protein eine MAP-Kinase-Kaskade sowie die Ras-abhängige Signalübertragung eingeleitet. Weitere kleine G-Proteine, aber auch Inositolphosphat-Signale und dadurch vermittelter Calcium-Einstrom sind an der intrazellulären Antwort beteiligt (Murry et al., 2019; Dissertation Reyna Murry, 2019). Zusätzliche cAMP-Bildung sowie die lokale Bildung von Cytoskelett-Verankerungen in der Membran, so genannte *lipid rafts*, sind alle an der sexuellen Entwicklung beteiligt. An diesen Membrandomänen ist das Cytoskelett verankert, das mit der Dynein-abhängigen Kernwanderung als Resultat einer Kreuzung befasst ist. Der Mechanismus der Kernunterscheidung kann bei Basidiomyceten besonders gut untersucht werden. So konnte Dynactin in einer Bachelorarbeit untersucht werden (Bachelorarbeit Ole Andersen, 2019).



Komponenten der intrazellulären Signaltransduktion und ihre Funktion bei *Schizophyllum commune*

Neben den Untersuchungen zur sexuellen Vermehrung werden Studien zur Beteiligung von *S. commune* an der Verwitterung von Gestein und Holz durchgeführt und Interaktionen mit anderen Pilzen und Bakterien untersucht. So konnten Mechanismen der biophysikalischen und biochemischen Verwitterung mit Schizophyllum gezeigt und in die einzelnen Komponenten zurlegt werden (Kirtzel et al., 2019 a, b).

Ektomykorrhiza

Fruchtkörper von *Tricholoma vaccinum* auf dem Testfeld bei Ronneburg

Besiedlungsstrategien und Interaktionen in der Ektomykorrhizosphäre wird am Beispiel des Bärtigen Ritterlings *Tricholoma vaccinum* untersucht. Die Genomsequenz und ein auf *Agrobacterium tumefaciens* basierendes Transformationssystem sollen durch CrispR/Cas-unterstützte Inaktivierung von Genen als Werkzeuge für funktionelle Untersuchungen weiter ausgebaut werden. Neben Genen, die zur Symbiose mit dem Wirtsbaum notwendig sind, werden Hydrophobine als sezernierte Zellwand-Proteine untersucht. Dabei zeigt sich immer wieder, dass Symbiose von mutualistischen bis zu parasitischen Interaktionen reicht – je nach Umweltbedingungen (Abdulsalam et al., 2019).

Besondes Schwermetalle, aber auch andere Stressfaktoren induzieren nicht nur Retrotransposons, sondern beispielsweise auch in unterschiedlichem Masse Glutathion-S-Transferase-Gene. Die Symbiose wird durch andere Bodenmikroorganismen beeinflusst (Wagner et al., 2019). So konnten Zygomyceten als Produzenten eines Aktivators der Produktion von Phytohormonen und Volatilen bestätigt werden. Der Einfluss der Mykorrhiza auf das Ökosystem Wald wird auch an schwermetallbelasteten Standorten untersucht, die die Ektomykorrhiza-Biodiversität und das Auftreten verschiedener Explorationstypen in Bezug auf die

Umweltbelastung analysiert. Axenische Co-Kulturexperimente werden durchgeführt, um den molekularbiologischen Hintergrund der Schwermetallantwort aufzuklären (Masterarbeit Anna Bonrath, 2019).

Bio-Geo-Interaktionen

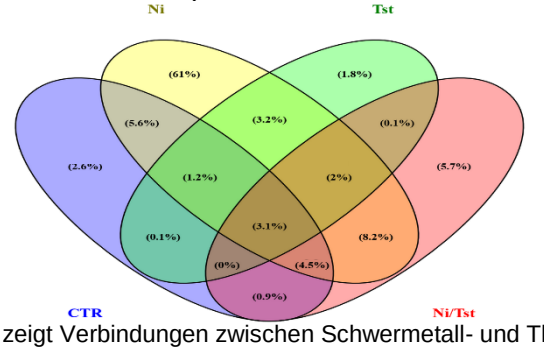
Als Outreach-Aktivität wurde 2019 ein Film (Tatortreiniger Pilze) in der mdr-Reihe Wissen veröffentlicht, der auf dem Testfeld bei Ronneburg während des Feldpraktikum Bio-Geo-Interaktionen II im Studienfang BSc Biogeowissenschaften gedreht wurde

Streptomyceten von einem schwermetallbelasteten Standort aus Ostthüringen werden untersucht, um Mechanismen Bio-Geo-Interaktionen am Beispiel dieser ehemaligen Uranbergbauregion zu charakterisieren. In Streptomyceten werden Physiologie und Schwermetallresistenz und deren genetischen Grundlagen mit molekularbiologischen Methoden genauer erforscht. Feld- und Topfversuche zusammen mit Pflanzen und Mykorrhizapilzen sollen Ansätze für eine Bioremediation belasteter Flächen erlauben. Die Mobilität von Schwermetallen und ihr Transport sowie der Einfluss der Bodenmikroorganismen wird in mehreren Projekten untersucht. Dabei war die Mobilität in Bedenproben Ausgangpunkt vieler Mikrokosmos-Experimente, die sterile Bodenproben benötigten (Krausse et al., 2019).

Ein weiterer Schwerpunkt ist die Untersuchung der bakteriellen Diversität verschiedener Habitate, auch im Hinblick auf die Geologie der Standorte, wie bspw. Huminsanden, der Vergleich verschiedener salzhaltiger Quellen des Thüringer Beckens oder Radionuklid-haltigen Wässern mehrerer Bergwerke. Auch das Mikrobiom eines ehemaligen Alaunschiefer-Bergwerks wurde untersucht und eine unerwartet reiche Pilzgemeinschaft identifiziert (Burow et al., 2019).

Weiterhin wird der Abbau von polyzyklischen aromatischen Kohlenwasserstoffen durch autochthone Mikroorganismen in kontaminierten Gaswerkstandorten analysiert - ebenfalls im Hinblick auf den Einsatz von Mikroorganismen für eine schonende Remediation belasteter Flächen.

Ein Schwerpunkt der Arbeiten liegt in der Einbindung in den Sonderforschungsbereich „ChemBioSys“. Hier werden Interaktionen zwischen Schwermetall- und Antibiotikastress am Beispiel des extrem Nickel-resistenten *Streptomyces mirabilis* P16-B1 und molekularen Antworten auf Thiostrepton untersucht (Masterarbeit Marlene Höller, 2019).



Das Proteom zeigt Verbindungen zwischen Schwermetall- und Thiostrepton-Antwort.

2. Publikationen

Abdulsalam O, Kothe E, Krause K. 2019. The parasitic-neutral-mutual continuum of plant-fungal interactions. J Appl Bot Food Qual 92, 246-249.

Burow K, Grawunder A, Harpke M, Pietschmann S, Ehrhardt R, Wagner L, Voigt K, Merten D, Büchel G, Kothe E. 2019. Microbiomes in an acidic rock-water cave system. FEMS Microbiol Lett 366, fnz167.

Kirtzel J, Scherwietes EL, Merten D, Krause K, Kothe E (2018) Metal release and sequestration from black slate mediated by a laccase of *Schizophyllum commune*. Environ Sci Pollut Res 26, 5-13.

Kirtzel J, Ueberschaar N, Deckert-Gaudig T, Krause K, Deckert V, Gadd GM, Kothe E. 2019. Organic acids, siderophores, enzymes and mechanical pressure for black slate bioweathering with the basidiomycete *Schizophyllum commune*. Environ Microbiol, doi: 10.1111/1462-2920.14749. [Epub ahead of print]

Kraußе T, Schütze E, Phieler R, Fürst D, Merten D, Büchel G, Kothe E (2019) Changes in element availability induced by sterilization in heavy metal contaminated substrates: A comprehensive study. J Hazard Mater 370:70-79.

Murry R, Kniemeyer O, Krause K, Saiardi A, Kothe E. 2019. Crosstalk between Ras and inositol phosphate signaling revealed by lithium action on inositol monophosphatase in *Schizophyllum commune*. Adv Biol Regul 72, 78-88.

Wagner K, Krause K, Gallegos-Monterrosa R, Sammer D, Kovács ÁT, Kothe E. 2019. The ectomycorrhizospheric habitat of Norway spruce and *Tricholoma vaccinum*: Promotion of plant growth and fitness by a rich microorganismic community. Front Microbiol 10, 307.

3. Drittmittelprojekte

Projektträger	**Vorhaben**	**Laufzeit**	**Mittel in 2019**
DFG	Sonderforschungsbereich ChemBioSys – Teilprojekt C03	01.07.2018-30.06.2022	13.000,00 € + 1 Doktorand
Max-Planck-Gesellschaft	International Max Planck Research School "global Biogeochemical Cycles"	2017 - 2020	1 Doktorandin
BMBF (Karlsruhe)	USER: Umsetzung von Schwermetall-Landfarming zur nachhaltigen Landschaftsgestaltung und Gewinnung erneuerbarer Energien auf radionuklidbelasteten Flächen	01.12.2014 – 31.05.2019	6.735,00 € (Anteil AG Kothe)
Gesellschaft für Anlagen- und Reaktorsicherheit (GRS) gGmbH	USER2 – Umsetzung von Schwermetall-Landfarming zur nachhaltigen Landschaftsgestaltung und Gewinnung	01.07.2019 – 30.06.2022	27.000,00 € + 2 Doktoranden
BMBF (Karlsruhe)	Verbundprojekt: Untersuchung des Potenzials biolgischer Verfahren zur Strahlenschutzvorsorge bei Radionuklidbelastungen (BioVeStRa)	01.06.2016 - 31.05.2019	42.972,00 € (Anteil AG Kothe)
Leibniz Science Campus (LSC) InfectoOptics	Verbundvorhaben “High end” optische Technologien zur Analyse intrazellulärer, membranbeeinflussender Infektionsprozesse – HoT-Aim 2.0	01.09.2019 - 31.08.2023	2.500,00 € + 1 Doktorandin
DAAD	Sachmittel- und Betreuungskostenzuschuss für DAAD Stipendiaten	01.03.2018-28.02.2020	1.000,00 €
Carl-Zeiss-Stiftung	“Jena School for Microbial Communication”	01.02.2017-31.01.2020	15.000,00 € + 1 Doktorand
DFG	Exzellenzcluster “Balance of the Microverse”		

4. Studium und Lehre

Angebotene Module der Mikrobiellen Kommunikation

Modulnummer	Veranstaltung	ECTS	Teilnehmerzahl
Wintersemester 2018/2019			
BB3.MB3	Praktikum Isolierung und Charakterisierung von Bodenmikroorganismen	10	9
	Seminar Aktuelle Methoden und Anwendungen		9
BBGW3.6/ LBio-Mbio/ BEBW4/ BEW2G3/ BBC2.2	Vorlesung Mikrobiologie	6	8 28 1 64 50
BBGW 1.4	Vorlesung Bio-Geo-Interaktionen	3	26
MMB003	Vorlesung Mikrobielle Interaktionen	10	38
	Praktikum Mikrobielle Interaktionen		38
	Seminar Mikrobielle Interaktionen		38
	Microbial Communication Colloquium		~50
MBGW1.1	Bio-Geo-Kolloquium	3	30
MBGW 1.3	Vorlesung/Übung/Seminar Bioremediation	5	9
MBGW 1.4.6	Praktikum Bodenmikrobiologie	6	5
	Seminar Organismische Interaktionen		~30
Sommersemester 2019			
BB1.5/BEBW4	Vorlesung Vielfalt mikrobieller Lebensformen	3	60
BBGW3.6	Praktikum Mikrobiologie für Biogeowissenschaften	3	3
BBGW 1.4 / 2	Seminar Bio-Geo-Interaktionen I/2	3	17
MMB001	Einführung in die Mikrobiologie		40
MMB1.1, 1.2,	Microbial Communication Colloquium		~50
MMB007	Basidiomyceten (Dr. Dörfelt)	10	20
	Praktikum Molekulare Kommunikation (inkl. Exkursion)		20
	Seminar Molekulare Kommunikation		20
MMB017	Praktikum Mikroben-Pflanze-Interaktionen (Dr. Agler)	10	16
	Seminar Mikroben-Pflanze-Interaktionen		16
	Übung Mikroben-Pflanze-Interaktionen		16
MBGW1.1	Bio-Geo-Kolloquium	3	30
BBGW 4.3	Bio-Geo-Interaktionen II	6	13
	Seminar Organismische Interaktionen		~30

Feldpraktikum im September 2019 auf dem Testfeld bei Ronneburg

Vertiefungs- und Projektmodule

	ECTS	Anzahl Studierende
Vertiefungspraktikum Mikrobiologie BB3.MB4	10	1
Biogeowissenschaftliches Projektmodul BBGW 6.3.2	10	6
Projektmodul MMB 3.1	15	6
Vertiefungsmodul MMB 3.2	15	6
Biogeowiss. Projektmodul 1	15	3
Biogeowiss. Projektmodul 2	15	0

Abschlussarbeiten

Bachelorarbeiten:
Ole Andersen: „Dynactin in *Schizophyllum commune*“ (Oktober 2019)

Zweitbetreuung/-gutachten:
Tim Richter: „Welche Merkmalsausprägungen müssen Arten aufweisen, um effektiv für Blühstreifen auf unterschiedlichen Standorten in der Agrarlandschaft Thüringens eingesetzt werden zu können?“ (Juli 2019)

Linda Langhans: “Anpassung an kalte Temperaturen von Makroalgen und Bakterien in der Antarktis” (September 2019)

Masterarbeiten:
Rabia Ülkü Korkmaz: “Function and biosynthesis of sesquiterpenes from *Schizophyllum commune*” (Januar 2019)

Anna Bonrath: „Characterization of potential *hydrophobin8* overexpressing transformants from the ectomycorrhizal fungus *Tricholoma vaccinum*“ (April 2019)

Marlene Höller: „Differential gene expression study of *Streptomyces* under nickel and thiostrepton stress“ (November 2019)

Zweitbetreuung/-gutachten:
Aishwarya Murali: “Control of gut microbiome by Lepidopteran pest *Spodoptera littoralis*” (Januar 2019)

Marius Faber: “Weiterführende phylogenetische und metabolische Analyse von *Pseudoxylaria spp*.” (Januar 2019)

Viola Zertani: „Einfluss von elementarem Eisen und Magnetit auf die Remediation von arsenhaltigen Böden mit *Festuca rubra*“ (September 2019)

Emily Ann Puckett: “Temperature and competition influence growth of ophiostomatoid fungi associated with the European spruce bark beetle” (Januar 2019)

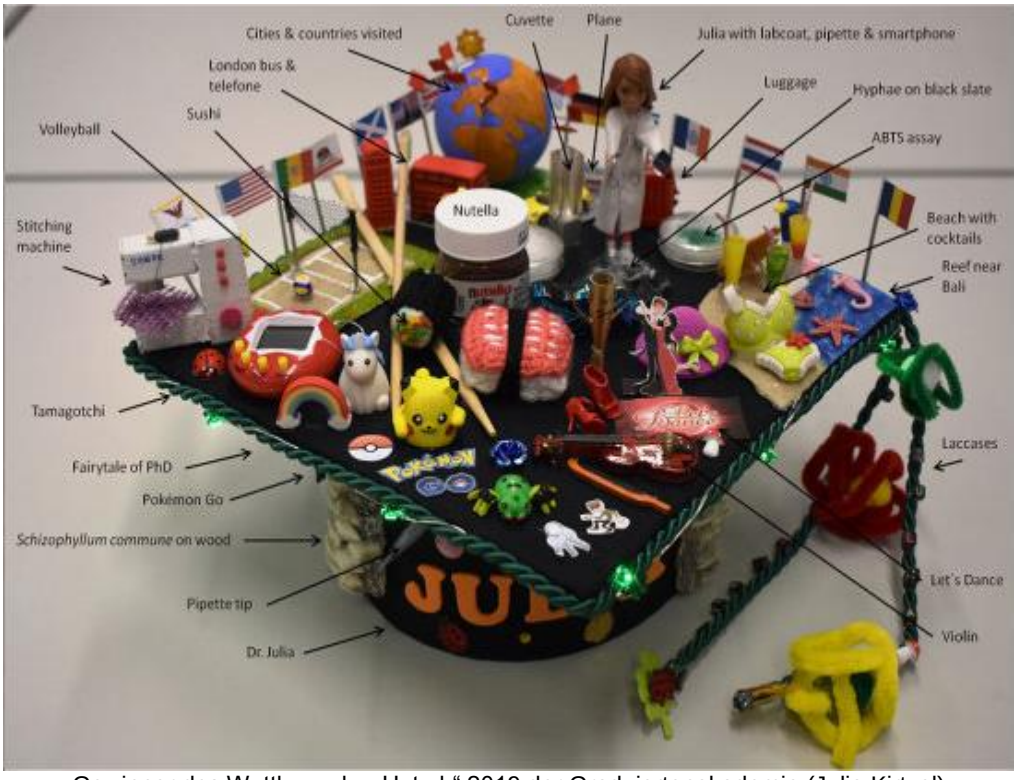
Sedef Özyürek: „Analysis of fungal-induced formation of auxin maxima in *Arabidopsis thaliana* roots“ (februar 2019)

Pamela Baumann: „Recovery and characterization of plant microbiome diversity via *in planta* isolation“ (März 2019)

Jan-Martin Daniel: „Biochemical and metabolomic studies on *Podaxis* sp.“ (September 2019)

Anindya Majumder: „Influence of beneficial fungi on NRT2.4 expression in *Arabidopsis thaliana* grown under stress condition“ (Dezember 2019)

5. Wissenschaftlicher Nachwuchs



Gewinner des Wettbewerbs „Hut ab“ 2019 der Graduiertenakademie (Julia Kirtzel)

Promotionsabschlüsse 2019

Sophia Wirth: “Volatilome of *Schizophyllum commune*”

Reyna Murry: „Inositol phosphate in the basidiomycete fungus *Schizophyllum commune*“

Marivic Martin: “Evolution of social interactions associated with matrix production in *Bacillus subtilis* biofilms”

6. Gleichstellung und Familie

Anteil Frauen	**Anteil Männer**	**Kindern unter 12 Jahren**
17	8	16
1 PostDoc, weiblich		1
2 Technische Assistentinnen		

7. Internationales

Kooperationen mit internationalen Universitäten

ENEA – Casaccia Research Centre – **Italien**

University of Bucharest – **Rumänien**

Babes-Bolyai University of Cluj-Napoca – **Romänien**

Jagiellonian University in Krakow – **Polen**

University of Vienna – **Österreich**

Örebro Universitet – **Schweden**

University of Cagliari – **Italien**

University of Tucumán & PROIMI – **Argentinien**

University of Debrecen – **Hungary**

Instituto Politécnico Nacional CICATA-QRO – **Mexiko**

State Ecological Academy in Kiew – **Ukraine**

Internationale Tagungsbesuche

18th Congress of European Mycologists, 16.09. – 21.09.2019, Warschau, Polen

3rd International Caparica Conference on Pollutant Toxic Ions and Molecules 2019, 04.11. – 07.11.2019, Carpacia, Portugal

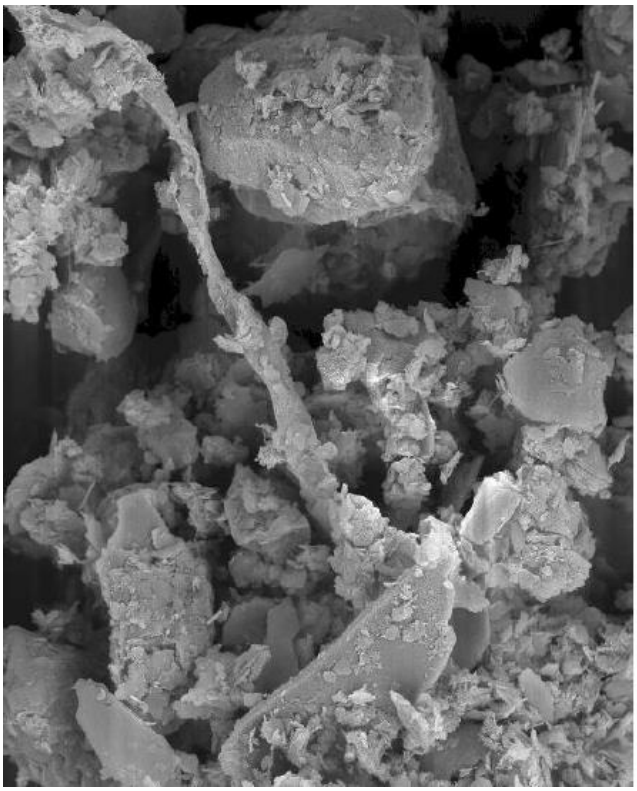
30th Fungal Genetics Conference, 12.03. – 17.03.2019, Pacific Grove, Californien

Auslandsaufenthalte Promovierender

Oluwatosin Abdulsalam: Gastaufenthalt für 3 Monate in Australien.

Sanierungskolloquium

Das 18. Jenaer Sanierungskolloquium hat vom 01.10.-02.10.2019 stattgefunden. Unter dem Titel „Structures matter in bio-geo interactions" waren ca. 100 nationale und internationale Gäste und MitarbeiterInnen im Haus zur Rosen zu Gast.



8. Administration/Finanzen

Beschäftigungsstruktur

	Personen	Stellenanteile
Beschäftigte im Rahmen von Haushaltsmitteln		
Wissenschaftliche MitarbeiterInnen	10	3,5
Profillinie Life	2	1,0
Technische Assistenz	2	2,0
Sekretariat	1	1,0
Tutorinnen	5	
Beschäftigte im Rahmen von Drittmitteln		
Wissenschaftliche MitarbeiterInnen	11	
Postdoc	1	
Wissenschaftliche Hilfskräfte	1	
Studentische Hilfskräfte	2	
Weiteres Personal		
Auszubildende	2	

Vertretung in Selbstverwaltungsgremien (Prof. Kothe)

Studiengangsleiterin MSc Microbiology
Mitglied der Prüfungskommission BSc/MSc Biogeowissenschaften
Sprecherin der Profillinie Life der FSU

Sprecherin des „Jena Center for Microbial Communication“ der FSU
Co-Sprecherin der Graduiertenschule Jena School for Microbial Communication
Präsidentin des Universitätsverbands zur Qualifizierung des wissenschaftlichen Nachwuchses in Deutschland "UniWiND"
Mitglied des Kuratoriums des Helmholtz-Zentrums Dresden-Rossendorf
Vorsitzende des Beirats des Leibniz Research Clusters „Bio/Synthetische Multifunktionale Produktionseinheiten“
Mitglied des Exekutivkommittees der International Max Planck Research School "global Biogeochemcial Cycles"
Mitglied der International Max Planck Research School "Molecular Ecology ", International Leibniz School "Molecular Microbial Interactions", DFG-SFB "ChemBioSys"; LeibnizCampus InfectoOptics; InfectoGnostics; Abbe Center of Photonics; HIGRADE
Editor-in-Chief: Journal of Basic Microbiology
Mitglied des Fachausschusses Mathematik und Naturwissenschaften der Akkreditierungsagentur Acquin
Vorsitzende der Findungskommission W3 „Molekulare Phytopathologie "

9. Team

Univ.-Prof. Dr. Erika Kothe

Stellvertretung

Dr. Katrin Krause

Technische Assistenz

Petra Mitscherlich
Peggy Brand-Schön

Verwaltung – Sekretariat

Christin Reichmann

Promovierende

Abdulsalam, Oluwatosin
Bogdanova, Olga
Brangsch, Hanka
Burow, Katja
Carl, Nina
Funai, Benjamin
Fürst, David
Höller, Marlene
Iyamu, Evans
Dr. Jung, Elke-Martina
Klose, Michael
Kraußе, Thomas
Lenk, Kevin
Östreicher, Manuela
Pietschmann, Sebastian
Pötschner, Jessica
Porsche, Berit-Frizzy
Stoiber-Lipp, Jennifer
Traxler, Lea
Wirth, Sophia

Studierende

Ahmad, Atif
Hayee, Abdul
Shrestha, Jenny
Weibchen, Nina

Lehraufträge

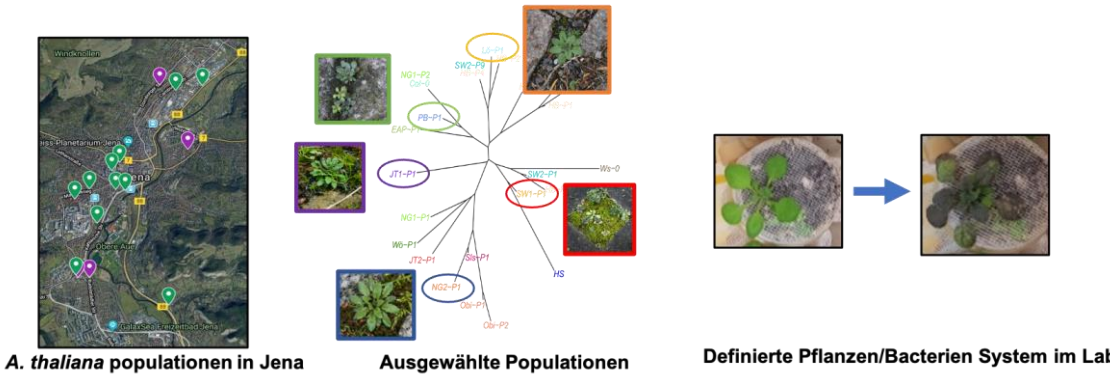
HDoz. Dr. Heiner Dörfelt

NWG „Plant Microbiosis“

(Dr. Matt Agler)

1. Forschung

Pflanzen sind einem ständigen Ansturm von Stressoren ausgesetzt, einschließlich der Invasion von Krankheitserregern. Obwohl Pflanzen ihre eigene Abwehr System haben (z.B., Wang et al., 2019), ist das richtige Gleichgewicht der Mikrobiota kritisch für das Überleben unter Stress (Vannier et al., 2019). Der Wirt *Arabidopsis thaliana* ist zum Beispiel sehr abhängig von kompetitiven Interaktionen zwischen Bakterien, Pilze und Oomyceten: Ohne



A.thaliana Populationen in Jena wurden gefunden und ihre Diversität untersucht. Definierte Kombinationen von Pflanzen und Mikrobielle Isolaten werden im Labor kultiviert, um zu verstehen wie Mikrobielle Interaktionen

diese Interaktionen überleben die Pflanzen nicht (Duran et al., 2018). Wir benutzen sowohl wilde Populationen von *A. thaliana* als auch andere Pflanzen arten, um zu verstehen, warum Bakterielle Eigenschaften entstehen und wie mikrobielle Interaktionen dadurch beeinflusst werden.

2. Publikationen

Wang Y, Garrido-Oter R, Wu J, Winkelmüller TM, Agler M, Colby T, Nobori T, Kemen E, Tsuda K. 2019. Site-specific cleavage of bacterial MucD by secreted proteases mediates antibacterial resistance in Arabidopsis. Nat Comm 10, 1-12.

Vannier N, Agler M, Hacquard S. 2019. Microbiota-mediated disease resistance in plants. PLoS Path 15; //dx.doi.org/10.1371/journal.ppat.1007740

3. Drittmittelprojekte

DFG	Balance of the Microverse Exzellenzkluster Teilproject	01.01.2020- 01.06.2023	10.000,00 €/j.+ 1 Doktorandin
DFG	JSMC Teilprojekt Graduiertenschule für Mikrobielle Kommunikation	01.3.2018 – 28.02.2021	10.000,00 /j.€+ 1 Doktorandin
Leibniz Gemeinschaft	ILRS Teilprojekte International Leibniz Research School	01.3.2018 – 28.02.2021	10.000,00 €/j.+ 1 Doktorandin

4. Studium und Lehre

Modulnummer	Veranstaltung	ECTS	Teilnehmerzahl
Sommersemester 2017/2018			
MMB2.7	Praktikum Pflanzen-Mikroben Interaktionen	5	18
	Seminar Pflanzen-Mikroben Interaktionen		18

Vertiefungs- und Projektmodule

	ECTS	Anzahl Studierende
Projektmodul MMB800	15	2
Vertiefungsmodul MMB700	15	2

Masterarbeiten

Pamela Baumann: „Recovery and characterization of plant microbiome diversity via *in-planta* isolation" (März 2019)

6. Gleichstellung und Familie

Anteil Frauen	Anteil Männer	Mit Kindern unter 12 Jahren
4	2	1

7. Internationales

Internationale Tagungsbesuche

OneHealth Summer School and Research Symposium, 12.08. – 14.08.2019, Bern, Schweiz.

9. Team

Promovierende

Mayer, Teresa

Murillo-Roos, Mariana

Jose, Jisna

Studierende

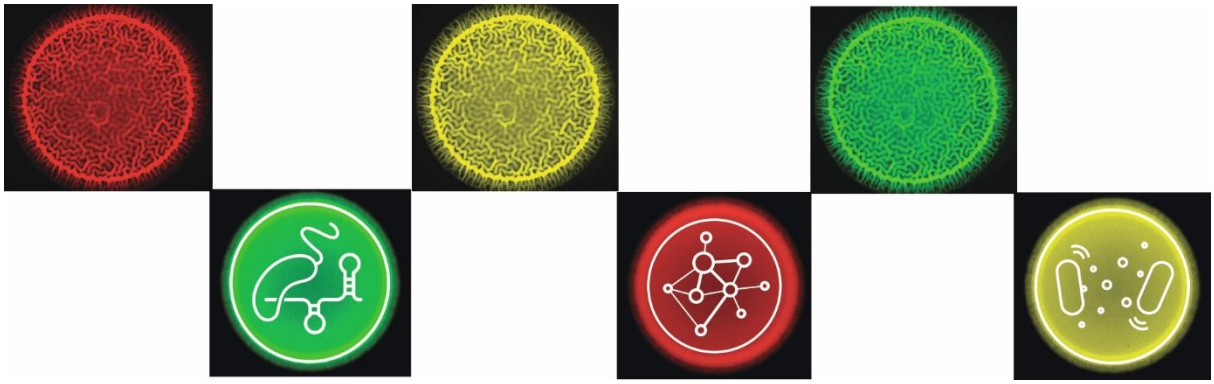
Abdullah, Muhammed

Unger, Kerstin

Odejide, Aminat

Lehrstuhl für Allgemeine Mikrobiologie

Prof. Dr. Kai Papenfort



Mission

The laboratory of General Microbiology (Allgemeine Mikrobiologie; www.papenfortlab.org) joined the University of Jena in October 2019. Our research focuses on two emerging topics in microbiology and infection biology: gene control by regulatory RNAs and microbial communication.

1. Research

Bacterial regulatory RNAs

Regulatory RNAs control gene expression in nearly all organisms. Supported by RNA-binding proteins, regulatory RNAs function by base-pairing with trans-encoded target mRNAs resulting in altered protein synthesis. In bacteria, small RNAs (sRNAs) constitute the best-studied class of non-coding regulators and have been estimated to control up to 20% of all genes in a given organism. We study the biological roles of sRNAs in microbial pathogens and how these affect fundamental processes such as communication, virulence and stress response. We are interested to understand the mechanistic underpinnings controlling sRNA-mediated gene regulation in bacteria, including the roles of auxiliary protein factors, e.g. RNA chaperones and ribonucleases, involved. Further, we are harnessing this information to design synthetic RNAs with specific regulatory functions.

Microbial communication

Intercellular communication is key to almost all life on Earth and provides the basis for the development of higher, multi-cellular organisms. Small diffusible molecules play an important role in this process and typically function as signals that convey information from one cell to another. We study intercellular communication in bacteria, a process commonly referred to as quorum sensing. Quorum sensing involves the production, release, and group-wide detection of extracellular signal molecules, which are detected by cognate receptors of vicinal cells. Processes controlled by quorum sensing, such as biofilm formation, secretion of virulence factors, and public goods production are unproductive when undertaken by a single bacterium but become effective when undertaken by the group. Consequently, quorum sensing is central to all microbiology as it enables otherwise solitary bacteria to coordinate complex cooperative tasks.

2. Publications (selected)

Peschek N, Hoyos M, Herzog R, Förstner KU, Papenfort K. 2019. A conserved seed-pairing domain affords small RNA-mediated stress resistance in enterobacteria. EMBO J 38, e101650.

Herzog R, Peschek N, Fröhlich KS, Papenfort K. 2019. Three autoinducer molecules act in concert to control virulence gene expression in Vibrio cholerae. Nucl Acids Res 47. 3171-3183.

Wucher BR, Hoyos M, Bartlett TM, Persat A, Papenfort K, Nadell CD. Filamentation of Vibrio cholerae is an adaptation for surface attachment and biofilm architecture. PNAS 116, 14216-14221.

Ben-Zvi T, Pushkarev A, Seri H, Elgrably-Weiss M, Papenfort K, Altuvia S. mRNA dynamics and alternative conformations adopted under low and high arginine concentrations control polyamine biosynthesis in Salmonella. PLoS Genet 15, e1007646.

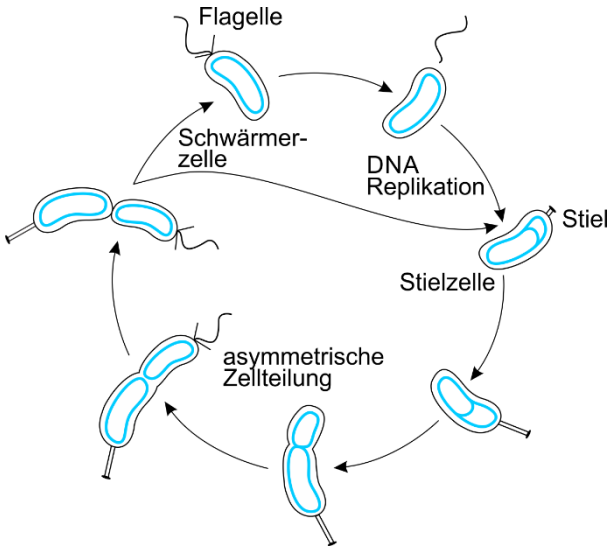
3. Third party funding (major)

Project Title	Funding source	Period
Synthetic small RNA regulators for tailored gene expression in bacteria	German Research Foundation (DFG-GRK2062)	2015 – 2019
The role of RNA-binding proteins for quorum sensing and virulence of V. cholerae	German-Israeli Foundation GIF (G241141613/2016)	2017 – 2019
Systems biology of bacterial small RNAs	Human Frontier Science Program (CDA00024/2016-C)	2016 – 2019
A threonine-derived communication system controls collective behaviors in Vibrio cholerae	German Research Foundation (DFG-PA2820/1)	2016 – 2019
Spatiotemporal dynamics of a membrane-bound RNA-binding protein and its cargo in Vibrio cholerae	German Research Foundation (DFG-TRR174)	2017 - 2020

µ-proteins and dual RNA regulators in Vibrio cholerae	German Research Foundation (DFG-SPP2002)	2017 - 2020
CIPSM (Center for Integrated Protein Science, Munich)	German Research Foundation (Exc114-2)	2017 – 2019
Harnessing small RNA biology to probe complex microbial phenotypes	Vallee Foundation	2019 -2023
Pyrazine Signalling in Commensal and Pathogenic Bacteria	ERC Starting Grant	2018 - 2022

NWG „RNA-Biologie der Bakterien“

(Dr. Kathrin Fröhlich)

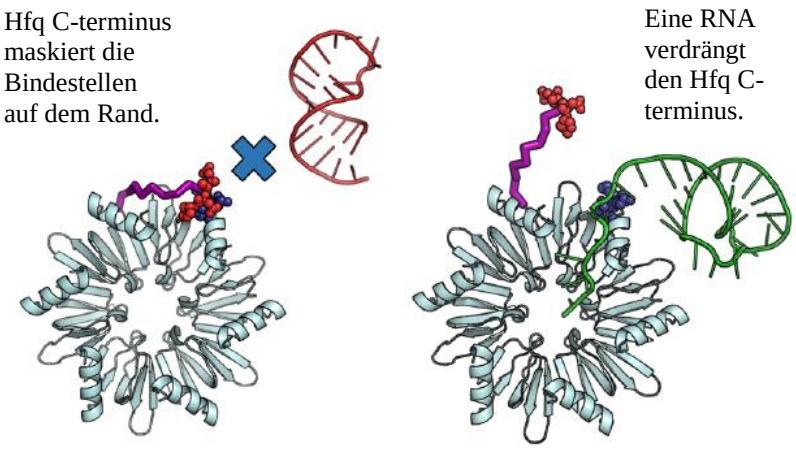


1. Forschung

Caulobacter crescentus ist ein in oligotrophen Gewässern beheimatetes Bakterium innerhalb der alpha-Proteobakterien. Eine Besonderheit dieser Spezies ist die intensiv untersuchte, asymmetrische Zellteilung (siehe Abbildung). Unter anderem nutzen wir in meiner Arbeitsgruppe *Caulobacter crescentus* als Modellorganismus um die Prinzipien der durch RNA regulierten Prozesse in alpha-Proteobakterien zu untersuchen, und neue Mechanismen der bakteriellen Genexpressionskontrolle zu identifizieren. Auf post-transkriptioneller Ebene sind kleine regulatorische RNAs (sRNAs) entscheidende Elemente der Genexpressionskontrolle in Bakterien. Die Mehrzahl der sRNAs kontrolliert Zieltranskripte über die Ausbildung direkter Basenpaarungen, welche zu Veränderung der Stabilität, der Prozessierung und der Translation der gebundenen mRNAs führen. Bakterielle sRNAs erlauben der Zelle, sich schnell an geänderte Umweltbedingungen anzupassen. Dabei sind sie besonders vielseitige Regulatoren, da sie die Genexpression sowohl aktivieren aber auch reprimieren können. Durch bioinformatische und experimentelle Studien wurden hunderte potenzieller sRNAs in den Genomen verschiedener bakterieller Spezies beschrieben, über deren Funktion und Mechanismen aber nur wenig bekannt ist.

Ein wichtiger Kofaktor für die Aktivität vieler sRNAs ist das RNA-Chaperon Hfq. Die Ringstruktur von Hfq, die sich durch den Zusammenschluss von sechs Monomeren ausbildet, erlaubt es einzelnen RNA Molekülen sowohl auf der Vorder- als auch auf der Rückseite der Ringoberfläche zu binden. Zusätzlich besteht die Möglichkeit, dass RNA mit dem Rand des Hexamers interagiert. Indem Hfq gleichzeitig sowohl die sRNA als auch deren Zieltranskript bindet, und diese in räumliche Nähe bringt, ermöglicht es die Interaktion beider RNAs. Aus theoretischen und *in vitro* Analysen entstand die Annahme, dass die freien C-termini der

einzelnen Monomere ebenfalls Kontakte mit den positiv geladenen Aminosäuren auf dem Rand des Ringes eingehen, und damit in Konkurrenz mit unspezifisch interagierenden RNAs treten können. Diese Theorie konnte nun dank der Aufklärung der vollständigen Kristallstruktur des Hfq Proteins aus *C. crescentus* untersucht, und ein Kontakt des C-terminus mit der Ringstruktur nachgwiesen werden (Santiago-Frangos A, Fröhlich KS, *Proc Nat Acad Sci* 116, 22).



Schematische Zusammenfassung zur Rolle des Hfq C-terminus in *C. crescentus*. An der Außenseite des Ringes gelegene, positiv geladene Aminosäuren (blau) können durch die Spitze des C-Terminus (in rot) abgeschirmt werden. Damit wird die unregulierte Assoziation von RNAs verhindert (linke Seite). Geeignete sRNAs sind in der Lage, den C-terminus zu verdrängen, und den Rand des Hfq Proteins zu binden (rechte Seite).

2. Publikationen 2019

Chuang SK, Vrla GD, Fröhlich KS, Gitai Z (2019) Surface association sensitizes *Pseudomonas aeruginosa* to quorum sensing. Nat Commun 10, 4118.

Bianco CM, Fröhlich KS, Vanderpool CK (2019) Bacterial cyclopropane fatty acid synthase mRNA is targeted by activating and repressing small RNAs. J Bacteriol 201.

Santiago-Frangos A, Fröhlich KS, Jeliazkov JR, Małecka-Grajek EM, Marino G, Gray JJ, Luisi BF, Woodson SA, Hardwick SW (2019) *Caulobacter crescentus* Hfq structure reveals a conserved mechanism of RNA annealing regulation. Proc Natl Acad Sci USA 116, 10978-10987.

Herzog R, Peschek N, Fröhlich KS, Schumacher K, Papenfort K (2019) Three autoinducer molecules act in concert to control virulence gene expression in *Vibrio cholerae*. Nucl Acids Res 47, 3171-3183.

3. Internationale Kooperationen

Zemer Gitai Z – Princeton University (US)
Cari Vanderpool – University of Illinois (US)
Sarah Woodson – Johns Hopkins University (US)
Ben Luisi – Cambridge University (UK)
Clare Kirkpatrik – University of Southern Denmark (DK)

Lehrstuhl für Mikrobielle Interaktionen

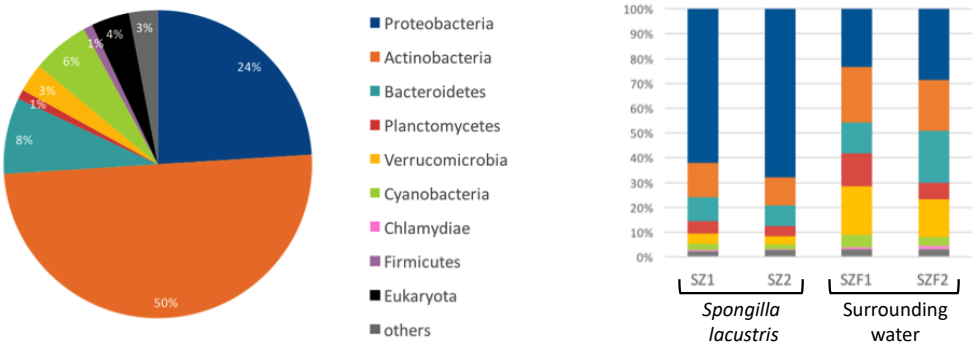
Prof. Dr. Christian Jogler

1. Forschung

The freshwater sponge microbiome and its interactions

Many, in particular aquatic habitats are still neglected. Here, we choose freshwater sponges as example. While marine sponges are intensively studied and these metaorganisms are known as rich sources for novel bacteria with interesting traits and novel small molecule production, surprisingly little is known about freshwater sponges.

To gain more insights into the freshwater sponge microbiome, cultivation independent analysis is required. While we usually compare the specific habitat (in this case the sponges) with the surrounding (here water), methods such as metagenomics or amplicon sequencing can be applied to determine the specific bacterial community composition.



Metagenomic- (left) and amplicon-based (right) analysis of the microbiome from the freshwater sponges.

Based on the bacterial community composition in a selected habitat, one knows which bacterial phyla are present. In the example of the *E. fluviatilis* metagenome, only 1% of the bacterial community composition were Planctomycetes. However, if selective enrichment strategies are applied, even strains from low abundant phyla can be cultivated.

In our proof of concept study, we enriched for Planctomycetes and obtained the novel species strain spb1. Interestingly, it forms more fibers compared to its closest relative, an important aspect which is currently used to determine the nature of the unusual crateriform structures in Planctomycetes.

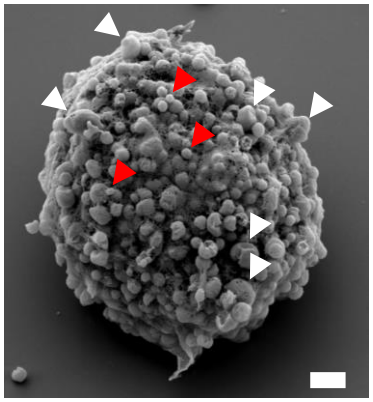
While targeted cultivation is useful for bacterial phyla with a few representatives, the untargeted approach is not biased by what we already know. In our proof of concept study, we employed a microdrop machine for semiautomated 96-well based cultivation. Basically, 50-200 cells are given into each well that is filled with a growth broth mimicking the natural habitat as close as possible (e.g. blended sponge extract). In parallel, other plates were inoculated with different media optimized for *de novo* cultivation.

The novel bacterial phylum Saltatorellota

We used artificial surfaces and exposed them to marine surroundings to figure out which organisms will colonize them. Given the great results from our plastic incubation experiments, we revisited this approach. We incubated microplastic filled chambers for two weeks in the Baltic Sea at Heiligendamm, Germany. Plastic particles were subsequently placed on appropriate petri dishes and novel pinkish bacteria grew.

We obtained three novel strains and first thought they might belong to the bacterial phylum Planctomycetes. After basic characterization and genome sequencing, we found the three novel species even to constitute a novel bacterial phylum. In-depth characterization resulted in unseen cell biology and major consequences for our understanding of the eukaryote evolution. Given the huge implications of our discovery, we asked all close collaborators for maximal critical review to

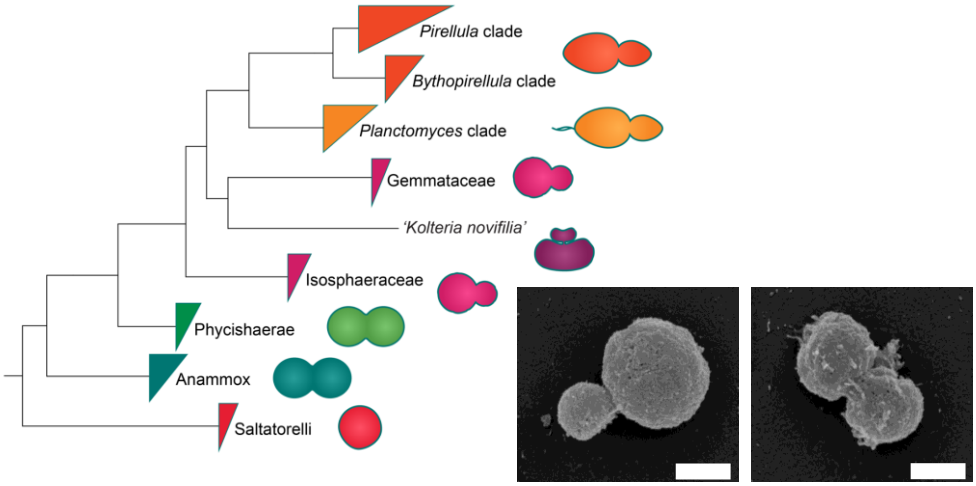
prepare a bullet proof publication: most colleagues took our findings for osmotic artefacts.



SEM analysis revealed that the aggregate forming species *Saltatorellus ferox* displays extreme polymorphism with giant amorphic- (white arrows) and small coccoid cells (red arrows, bar 3 µm).

We sampled a transect across the Baltic Sea and performed amplicon sequencing to determine the bacterial community composition in each water sample. Different areas of the Baltic Sea comprise very different salinities from 4 – 9 PSU. Thus, basically from fresh- to salt-water. Pinkish dots plotted on the salinity gradient represent the relative abundance of *Saltatorelli* (how many % of the bacterial community are members of the novel phylum *Saltatorelli*). Given that members of the novel phylum Saltatorelli occur basically in freshwater and in saltwater, osmotic fragility can be excluded. However, we performed control experiments at the different salinities as well. To exclude this possibility, we investigated the distribution of Saltatorelli among the salinity gradient of the Baltic Sea. The novel bacterial phylum *Saltatorelli* that we discovered is so exceptional that only the most striking aspects could be covered here: Cells form heterogeneous aggregates with very different cell size and shape.

The novel phylum *Saltatorelli* is part of the PVC-Superphylum and closely related to the phylum Planctomycetes. Different species of the phylum Planctomycetes can divide either via polar budding, or via binary fission. Both modes of cell division lack the major bacterial cell division protein FtsZ along with 10 further canonical bacterial divisome proteins.

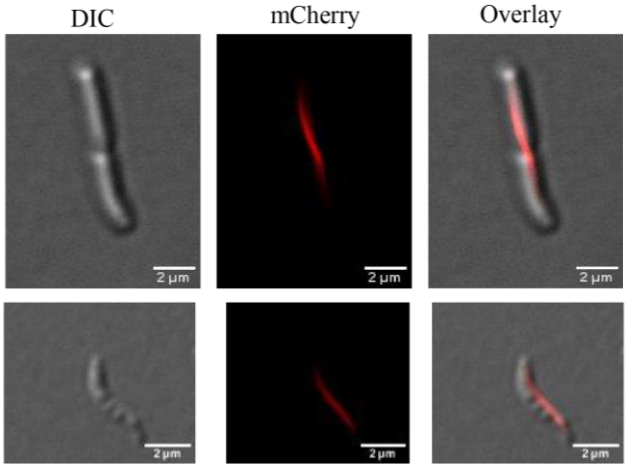


Saltatorelli are closely related to the phylum *Planctomycetes*. While different planctomycetal species divide either through budding, or via binary fission, a single species of the phylum *Saltatorelli* can do both (bar 500 nm).

In contrast, members of the novel phylum *Saltatorelli* can do both: divide by binary fission and polar budding, while their genomes lack FtsZ as well as most other canonical bacterial cell division related genes. To further investigate this unseen behavior, we performed time-laps microscopy with living cells and our observations became even more spectacular.

While the same cell can divide first via polar budding and second via binary fission, in particular the fusion of two cells is unseen among bacteria. Such a fusion might have been key during symbiogenesis, the uptake of a proteobacterium that eventually became the mitochondrium. However, such cell biological traits were thought to be impossible in ‘primitive’ prokaryotic cells. Along these lines, amoeba-like locomotion or shape shifting are traits associated with eukaryotic hallmark traits such as a complex actin-based cytoskeleton and motor proteins that are absent among bacteria. However, the novel phylum *Salltatorelli* can perform amoeba-like movement and crawl on surfaces. Furthermore, the species Saltatorellus ferox can form trunk-like extensions of the cell body within minutes. Such extensions were frequently observed among very large cells with a diameter of 5-15 µm.

The shapeshifting among *Saltatorelli* is not limited to the formation of trunk-like extensions. Entire cells can vary their shape within minutes such as during amoeba-like movement. Sometimes such movements do not span a large distance but seem more the consequence of shapeshifting for yet unknown reasons.All this strange cell biology of *Saltatorelli* parallels to some extend L-form bacteria. These are artificial osmotic fragile wall-less bacteria. However, *Saltatorelli* are not at all osmotically fragile. Furthermore, they possess a peptidoglycan cell wall like all other free-living bacteria. Analyzing the *Saltatorelli* genomes we identified unusual actin homologues that might be involved in the unusual observed traits. The MamK homology of saltatorellin might indicate that saltatorellin forms dynamic filaments, too. To put this hypothesis to test, we expressed a mCherry tacked saltatorellin from *Saltatorellus ferox* in *E. coli* and observed filament formation.



If the actin homologue saltatorellin is labeled with mCherry, it forms filaments in *E. coli* (upper panel). If the same construct is expressed in the magnetotactic organism *Magnetospirillum gryphiswaldense* (lower panel), saltatorellin forms filaments paralleling MamK, the dynamic actin-like filament of magnetotactic bacteria that actively positions the magentosme chain via treadmilling. Saltatorellin forms such filaments in a ΔMamK deletion mutant and complements MamK.

If the saltatorellin mCherry fusion was expressed in a ΔMamK deletion mutant of Magnetospirillum gryphiswaldense, if formed filaments, too and even complemented the lack of MamK, indicating a somehow similar function of both filaments. Our current hypothesis is that saltatorellin might be involved in shape-shifting and trunk formation via treadmilling of a filamentous structure with peptidoglycan as fixture.

Evolutionary implications

Our findings have implications for fields other as cell biology as well: It is a long standing believe in evolutionary biology, that the first endosymbiotic event –the uptake of a bacterium that eventually became the mitochondrion- was an absolute requirement to develop the typical eukaryotic traits due to energy restrictions. The novel phylum *Saltatorelli* challenges this

hypothesis as cells can shapeshift, move and even fuse in ways only eukaryotic cells were thought to be able to.

2. Publikationen

Wiegand S, Jogler M, Boedeker C, Pinto D, Vollmers J, Rivas-Marín E, Kohn T, Peeters SH, Heuer A, Rast P, Oberbeckmann S, Bunk B, Jeske O, Meyerdierks A, Storesund JE, Kallscheuer N, Lücker S, Lage OM, Pohl T, Merkel BJ, Hornburger P, Müller RW, Brümmer F, Labrenz M, Spormann AM, Op den Camp HJM, Overmann J, Amann R, Jetten MSM, Mascher T, Medema MH, Devos DP, Kaster AK, Øvreås L, Rohde M, Galperin MY, Jogler C. 2019. Cultivation and functional characterization of 79 planctomycetes uncovers their unique biology. Nature Microbiol 5, 126-140.

Kallscheuer N, Wiegand S, Peeters SH, Jogler M, Boedeker C, Heuer A, Rast P, Jetten MSM, Rohde M, Jogler C. 2019. Description of three bacterial strains belonging to the new genus *Novipirellula* gen. nov., reclassificiation of *Rhodopirellula rosea* and *Rhodopirellula caenicola* and readjustment of the genus threshold of the phylogenetic marker *rpoB* for Planctomycetaceae. Antonie van Leeuwenhoek, doi: 10.1007/s10482-019-01374-5. [Epub ahead of print]

Kallscheuer N, Jogler M, Wiegand S, Peeters SH, Heuer A, Boedeker C, Jetten MSM, Rohde M, Jogler C. 2019. Three novel *Rubripirellula* species isolated from plastic particles submerged in the Baltic Sea and the estuary of the river Warnow in northern Germany. Antonie van Leeuwenhoek. doi: 10.1007/s10482-019-01368-3. [Epub ahead of print]

Boersma AS, Kallscheuer N, Wiegand S, Rast P, Peeters SH, Mesman RJ, Heuer A, Boedeker C, Jetten MSM, Rohde M, Jogler M, Jogler C*). 2019. *Alienimonas californiensis* gen. nov. sp. nov., a novel Planctomycete isolated from the kelp forest in Monterey Bay. Antonie van Leeuwenhoek. doi: 10.1007/s10482-019-01367-4. [Epub ahead of print]

Kallscheuer N, Wiegand S, Jogler M, Boedeker C, Peeters SH, Rast P, Heuer A, Jetten MSM, Rohde M, Jogler C. 2019. *Rhodopirellula heiligendammensis* sp. nov., *Rhodopirellula pilleata* sp. nov., and *Rhodopirellula solitaria* sp. nov. isolated from natural or artificial marine surfaces in Northern Germany and California, USA, and emended description of the genus *Rhodopirellula*. Antonie Van Leeuwenhoek. doi: 10.1007/s10482-019-01366-5. [Epub ahead of print]

Kohn T, Wiegand S, Boedeker C, Rast P, Heuer A, Jetten MSM, Schüler M, Becker S, Rohde C, Müller RW, Brümmer F, Rohde M, Engelhardt H, Jogler M, Jogler C. 2019. *Planctopirus ephydatiae*, a novel Planctomycete isolated from a freshwater sponge. Syst Appl Microbiol 11, 126022.

Kallscheuer N, Jogler M, Wiegand S, Peeters SH, Heuer A, Boedeker C, Jetten MSM, Rohde M, Jogler C. 2019. *Rubinisphaera italica* sp. nov. isolated from a hydrothermal area in the Tyrrhenian Sea close to the volcanic island Panarea. Antonie van Leeuwenhoek. doi: 10.1007/s10482-019-01329-w. [Epub ahead of print]

Kallscheuer N, Moreira C, Airs R, Llewellyn CA, Wiegand S, Jogler C, Lage OM. 2019. Pink- and orange-pigmented Planctomycetes produce saproxanthin-type carotenoids including a rare C45 carotenoid. Environ Microbiol Rep 11, 741-748.

3. Studium und Lehre

Angebotene Module der Mikrobiellen Interaktionen

MMB004: Microbial Interactions

4. Gleichstellung und Familie

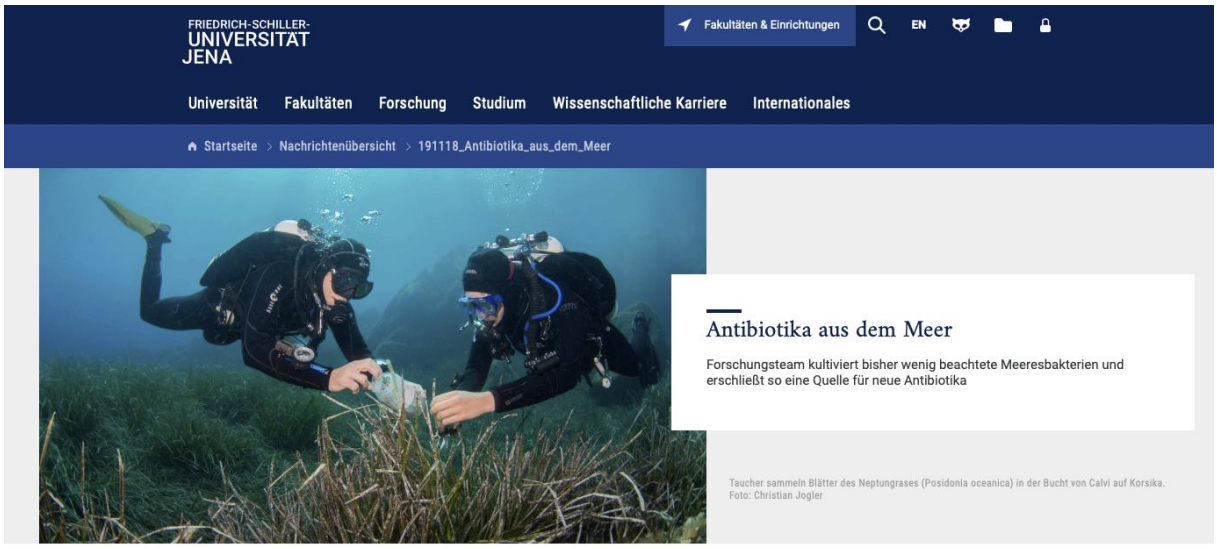
6 weibliche und 6 männliche

5. Team (Mitglieder über beide Standorte)

Leitung
Prof. Dr. Christian Jogler
Stellvertretung
Dr. Sandra Studenik
Dr. Mareike Jogler
PostDocs
Dr. Sandra Wiegand (Standort Nijmegen, NL, startete ihre eigene Arbeitsgruppe im Dezember 2019)
Dr. Nicolai Kallscheuer (Standort Nijmegen, NL)
Technische Assistenz
Nicole Wohlfarth
Anke Hinsching
Verwaltung – Sekretariat
Sabine Schein
Promovierende
Timo Kohn (Standort Nijmegen, verteidigte am 08.10.2019 in der Radboud Universität Nijmegen, NL)
Stijn Peeters (Standort Nijmegen, NL)
MSc Studenten
Markus Salbreiter
Muhammad Waqqas

6. Pressemitteilungen

https://www.uni-jena.de/191118_Antibiotika_aus_dem_Meer



NWG „Anaerobe Mikrobiologie“

(Dr. Torsten Schubert)

1. Forschung

Die Forschung der seit 10/2019 bestehenden Arbeitsgruppe beschäftigt sich mit anaeroben Prozessen. Vitamin B_{12}-haltige Enzyme übernehmen zentrale Rollen im Energie- und Baustoffwechsel anaerober Mikroorganismen. Die phylogenetisch diverse Gruppe der reduktiv dehalogenierenden Bakterien nutzt Cobamide (B_{12}-Vitamere) als Kofaktoren des Schlüsselenzyms der Energiekonservierung, die respiratorische reduktive Dehalogenase. Dieses Membran-gebundene Eisen-Schwefel-Protein fungiert als terminale Reduktase in einer Atmungskette, welche die enzymatische reduktive Dehalogenierung an den Aufbau eines chemiosmotischen Protonenpotentials koppelt (Organohalid-Respiration).

Die Arbeitsgruppe untersucht die Zusammensetzung und Funktionsweise der Organohalid-Atmungskette in reduktiv dehalogenierenden Bakterien. Des Weiteren wird die Struktur und Funktion reduktiver Dehalogenasen erforscht. Die Aufdeckung der Rolle des Cobamid-Kofaktors in der Katalyse, seine Akquise und Strukturvariabilität in verschiedenen Vertretern stellt einen weiteren Teil unserer Forschung dar. Wir untersuchen den Mechanismus der Sensierung von halogenierten organischen Verbindungen, welche die Expression von Genen mit funktionellem Bezug zur Organohalid-Respiration steuert. Die Resultate unserer Forschung werden molekulare Details einer wenig erforschten Form der anaeroben Atmung offenlegen, welche auf der Reaktivität von Cobamiden beruht.

2. Publikationen

Schubert T, von Reuß SH, Kunze C, Paetz C, Kruse S, Brand-Schön P, Nelly AM, Nüske J, Diekert G. 2019. Guided cobamide biosynthesis for heterologous production of reductive dehalogenases. Microb Biotechnol 12, 346-359. doi:10.1111/1751-7915.13339.

Türkowsky D, Lohmann P, Mühlenbrink M, Schubert T, Adrian L, Goris T, Jehmlich N, von Bergen M. 2019. Thermal proteome profiling allows quantitative assessment of interactions between tetrachloroethene reductive dehalogenase and trichloroethene. J Proteomics 192, 10-17. doi:10.1016/j.jprot.2018.05.018.

Keller S, Wetterhorn KM, Vecellio A, Seeger M, Rayment I, Schubert T. 2019. Structural and functional analysis of an L-serine O-phosphate decarboxylase involved in norcobamide biosynthesis. FEBS Lett 593, 3040-3053. doi:10.1002/1873-3468.13543.

3. Öffentlichkeitsarbeit

New Potentials of Biocement (F. Gerlach, J. Huhnholz, Bauhaus Universität Weimar, Produktdesign

Links: https://www.youtube.com/watch?v=DsGMBxbaX2M
https://www.uni-weimar.de/de/universitaet/aktuell/jaehrliche-veranstaltungen/archiv/jaehrliche-veranstaltungen-2019/summaery2019/projekte/?tx_showcase_summaeryprojectpublic%5Bproject%5D=1751&tx_showcase_summaeryprojectpublic%5Baction%5D=show&tx_showcase_summaeryprojectpublic%5Bcontroller%5D=Summaery&cHash=8df468c54722607c4a82e655cb6fadc7

4. Team

Dr. Torsten Schubert (Leitung), Dr. Sandra Studenik (Wissenschaftliche Mitarbeiterin)

Lehrstuhl für Molekulare Mikrobiologie

Prof. Dr. Axel Brakhage

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

1. Research

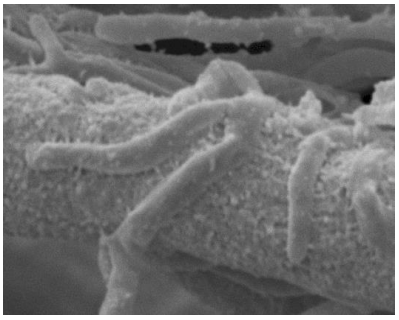
Prof. Brakhage is head of the chair of Molecular Microbiology and leads the Department of Molecular and Applied Microbiology (MAM) at the Leibniz Insitute for Natural Product Research and Infection Biology (HKI). The research of his group is devoted to the two main areas of the HKI, i.e., infection biology of fungi and natural product research. The Department is organised in several research teams reflecting the research areas:

- Infection biology of *Aspergillus fumigatus* - Host-pathogen interactions, new strategies for treatment
- Molecular biotechnology / synthetic biology of natural products
- Natural products as chemical language for microbial communication and virulence determinants
- Functional microbiome research
- Eukaryotic transcription factors and signal transduction

Aspergillus fumigatus has become the most important airborne fungal mould in humans. It causes different diseases ranging from allergies, to systemic, life-threatening infections. Individuals at risk for developing invasive aspergillosis are immunocompromised patients. Invasive aspergillosis is associated with high mortality because diagnostic and therapeutic options are inefficient. Furthermore, the pathophysiology of *A. fumigatus* infections is poorly understood. Scientists of the MAM study diverse aspects of the biology and virulence of *A. fumigatus* including signal transduction, the biosynthesis of secondary metabolites, the improvement of genomics, transcriptomics and proteomic tools and analyse the host-pathogen interaction.

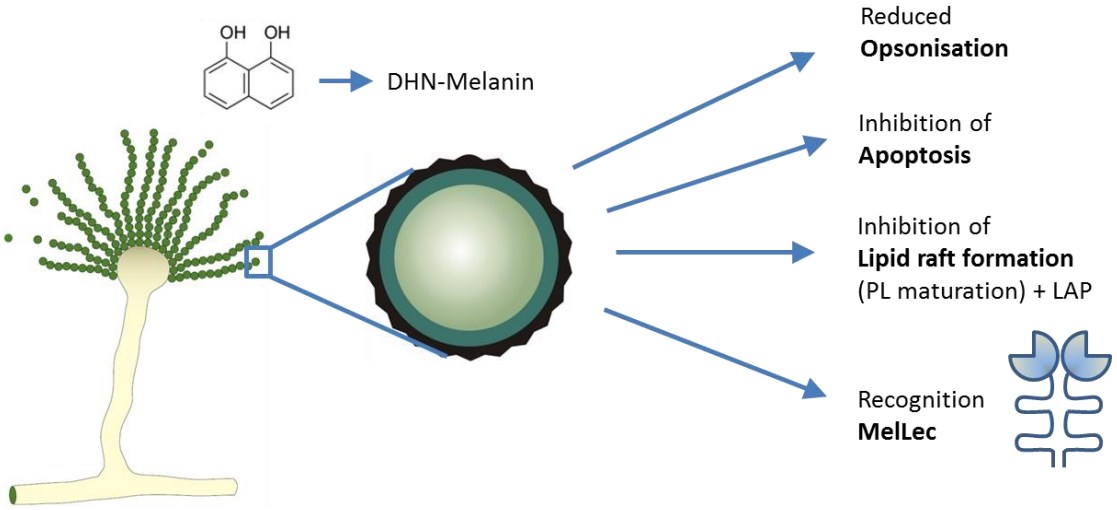
Fungi produce numerous secondary metabolites including mycotoxins and antibiotics. By using *Aspergillus nidulans* as a model organism but also the pathogen *A. fumigatus* the Department uncovers the regulatory pathways and physiological conditions, which lead to the biosynthesis of secondary metabolites, which at the same time can respresent virulence factors. In collaboration with other Departments of the HKI we focus on the search and characterisation of new secondary metabolite gene clusters and their molecular regulation. In this context, we have discovered a novel principle of activation based on the interaction of *A. nidulans* with a Gram-positive soil bacterium, *Streptomyces rapamycinicus,* which reprograms the fungal histone modification machinery.

More information about the group can also be found on the following webpage:
https://www.leibniz-hki.de/de/molekulare-und-angewandte-mikrobiologie.html



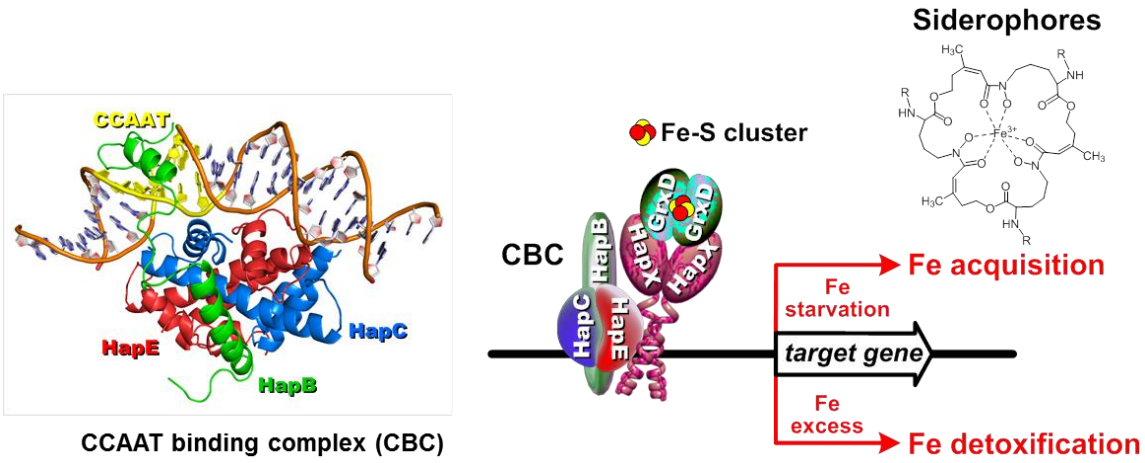
Infection biology of Aspergillus fumigatus – Host-pathogen interaction

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. The pigment dihydroxynaphthalene (DHN)-melanin that covers the surface of spores plays an important role in the virulence of *A. fumigatus* by protecting conidia from the adverse environment of phagolysosomes in macrophages. We now discovered the importance of flotillin-dependent lipid rafts for defence against *A. fumigatus* infections and that these lipid rafts are dysregulated by DHN-melanin (*bioRxiv 2019/Cell Reports 2020*). 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 (*Nature* 2018).



The human-pathogenic fungus *Aspergillus fumigatus* produces the dihydroxynaphthalene (DHN) melanin, which is a virulence factor. Its multifaceted effects are summarized.

Besides melanin, iron is a key regulator in host-pathogen interaction. The bZIP regulator HapX is the major regulator of iron homeostasis in *A. fumigatus*. By a co-immunoprecipitation approach and additional experiments we demonstrated that HapX requires the interaction with the monothiol glutaredoxin GrxD for iron sensing (*PLoS Genet* 2019). This study provides a new important factor in the regulatory circuit of iron homeostasis.



The post-translational regulatory function of *A. fumigatus* GrxD in iron regulation mediated by HapX. In -Fe conditions, HapX represses genes involved in iron-dependent pathways to save iron and activate iron acquisition. Both HapX functions require the HapB/HapC/HapE complex (CCAAT-binding complex) as DNA-binding scaffold, and the monothiol glutaredoxin GrxD that simultaneously activates the HapX iron-starvation function. Notably, GrxD is dispensable for the HapX iron detoxification function as HapX is able to sense iron levels independent of GrxD by FeS cluster incorporation.

In co-operation with the Department of Infection Biology we showed that the glycolytic enzyme enolase also acts as a surface ligand for human plasma complement regulators, which results in immune evasion (*Front Immunol* 2019). The mycotoxin gliotoxin, which is produced by *A. fumigatus*, is a known virulence factor. In a joint publication with the Institute of Pharmacy of the University of Jena (Oliver Werz) we provided evidence that gliotoxin suppresses the biosynthesis of the potent neutrophil chemoattractant leukotriene (LT)B_4 by direct interference with LTA_4 hydrolase and thus impairs neutrophil functions (*Cell Chem Biol* 2019).

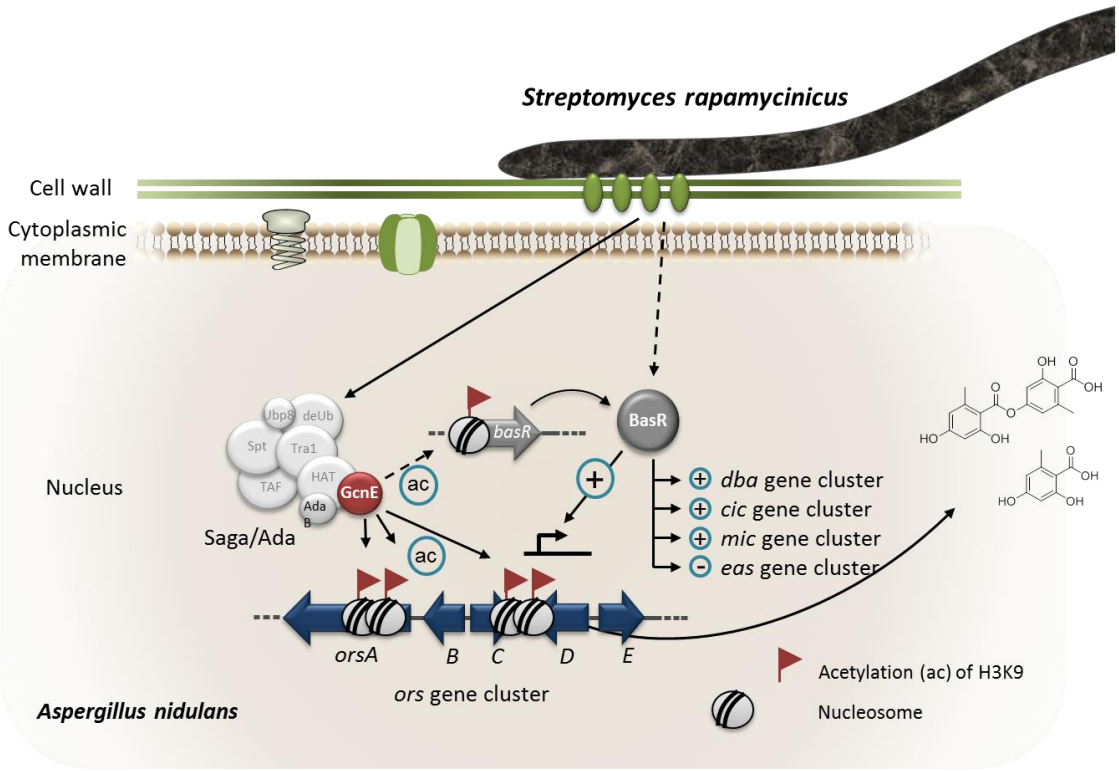
In comparison to the innate immune system, less is known about the adaptive immune response to fungal infections. In a joint project with Alexander Scheffold (University of Kiel) and Bernhard Hube (HKI) we identified the yeast *Candida albicans* as the main driver of the Th17 response against fungi in humans. Th17 cells directed against other fungi, including *A. fumigatus*, are induced almost exclusively by cross-reactivity to *C. albicans* (*Cell* 2019). Interestingly, Th17 cells reactive to *A. fumigatus* are selectively activated and expanded in patients with airway inflammation, in particular during acute allergic bronchopulmonary aspergillosis, a

hypersensitivity response in patients with predisposing lung diseases, e.g. asthma and cystc fibrosis.

A rapidly developing field in MAM is work on extracellular vesicles produced by neutrophils, macrophages, and epithelial cells against *A. fumigatus* (*bioRxiv* 2019, mBio 2020). Using this approach, we might have discovered an important contributor to the fungicidal activity of human neutrophils against *A. fumigatus* that might be of importance for improving therapy.

Natural products as chemical language for microbial communication and virulence determinants

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 *A. nidulans* leads to the activation of silent natural product biosynthetic gene clusters in the fungus). Our work showed that this phenomenon is triggered by chromatin modifications, in particular by H3 acetylation. These findings led to the novel concept that bacteria are able to manipulate the chromatin modification machinery of eukaryotes. 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*/*S. 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 attempt to expand this bipartite system to a tripartite system. 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).



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*., 2018; *eLife*).

2. Publications

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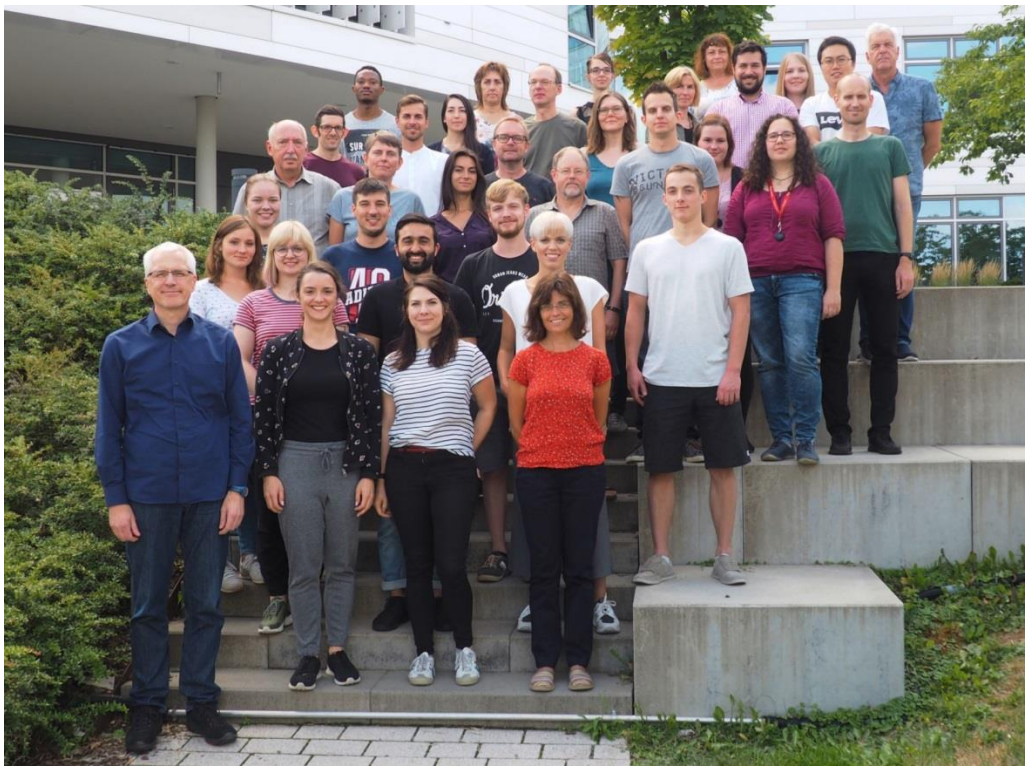
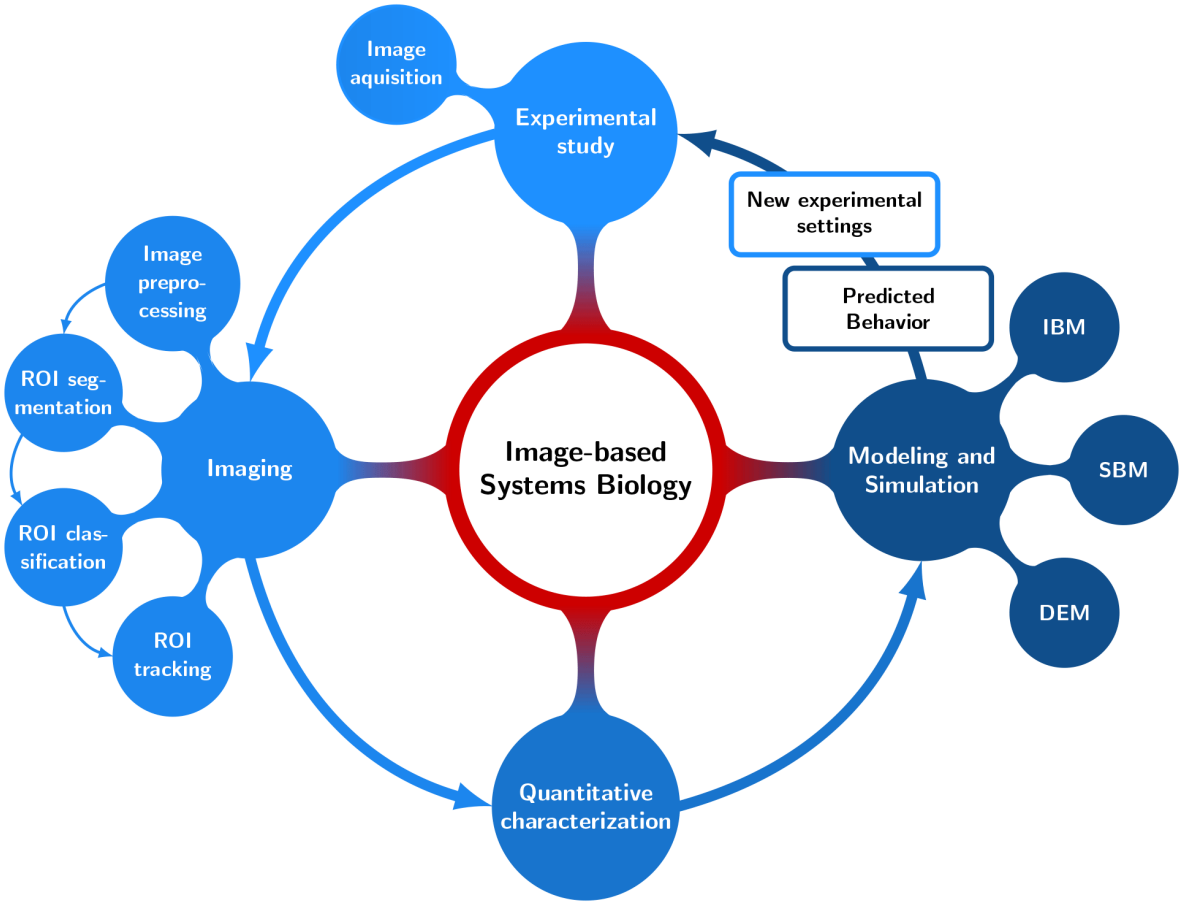
3. Team





Angewandte Systembiologie

Prof. Dr. Marc Thilo Figge

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

1. Research

The research group Applied Systems Biology is concerned with the mathematical modeling and computer simulation of infection processes caused by human-pathogenic fungi. The spatio-temporal data basis for these models is acquired by automatizing the data analysis of microscopy images on infection processes for high-throughput scanning. Our aim is to unravel secrets of the dynamical, functional and morphological aspects of the host-pathogen interaction using approaches of image-based systems biology.

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 (Svensson CM, et al. *Small* 2019). Thus, as depicted in Figure 1, 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).

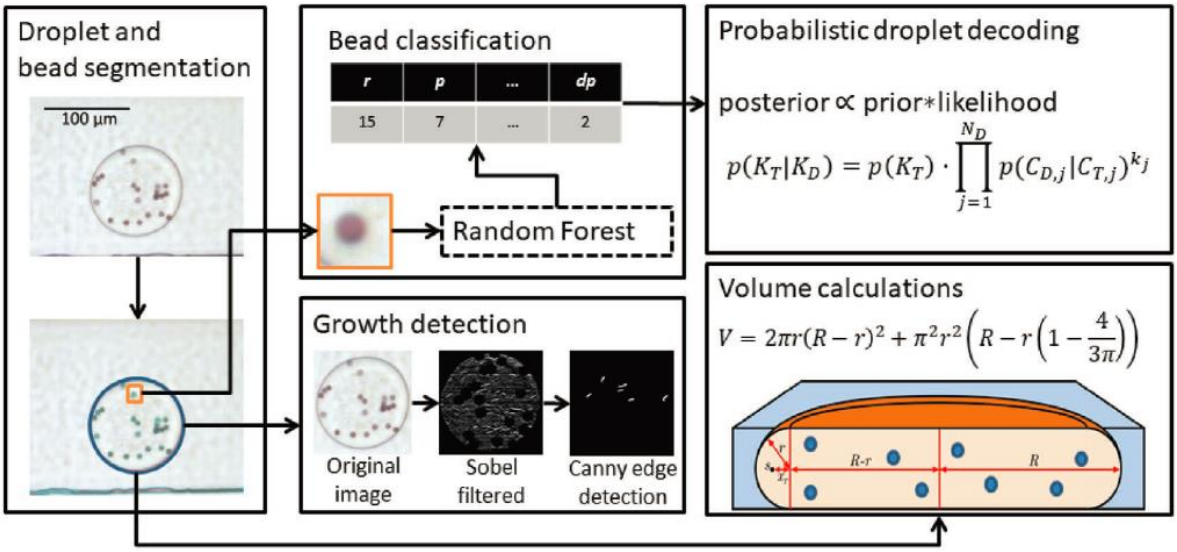


Figure 1: Workflow of droplet and bead segmentation and classification.

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 Molecular and Applied Microbiology 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 (Al-Zaben N, et al. *Scientific Reports* 2019) and the algorithm for confrontation assay quantification (ACAQ) of label-free cells based on a morphological filter approach (Cseresnyes Z, et al. *Cytometry A* 2018). This newly developed version of ACAQ was applied to the comparative analysis of phagocytosis assays confronting 17 worldwide-distributed strains of *Lichtheimia* species with alveolar macrophages. In collaboeration 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 (Hassan MIA, et al. *Environ*

Microbiol 2019). Both algorithms, AMIT and ACAQ, will play central roles in future analyses of microscopy data generated within the collaborative research center PolyTarget 1278 “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 (Meinel C, et al. *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 (Dasari P, et al. *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 (Dasari P, et al. *Front Immunol* 2019).

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 (Schaarschmidt B, et al. *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 and Jena (Dennhardt S, et al. *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 programing 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. As shown in Figure 2, 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 (Maurer M, et al. *Biomaterials* 2019). This analysis platform for microscopy data of *organ-on-chip* models will be further developed in newly started projects within the Excellence Cluster “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.

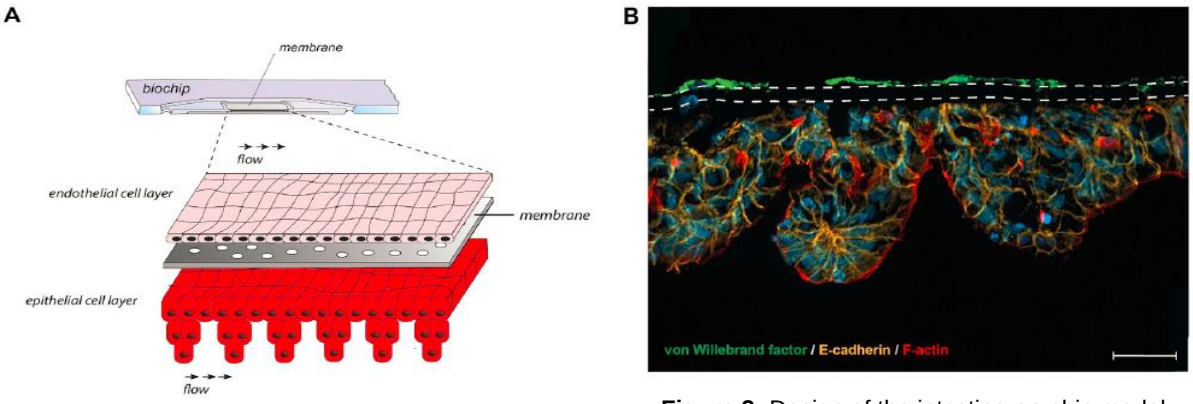


Figure 2: Design of the intestine-on-chip model featuring organotypic microanatomy. A) A porous membrane suspended in the biochip serves as a scaffold for the multi-layered intestinal model composed of endothelial and epithelial cells. Microchannels integrated into the biochip separately perfuse both epithelial and endothelial layers at 50 µl/min. B) Cross-section of the three-dimensional intestinal model.

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 (Prausse M, et al. *Front Immunol* 2018) as well as agent-based modeling (Timme S, et al. *Front Immunol* 2018) to simulate interactions at the molecular and cellular level. For example, within the collaborative research center FungiNet 124/2 “Pathogenic fungi and 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 hybird agent-based model (see Figure 3) for the comparative assessement of aspergillosis in the murine and human lung by virtual infection modeling (Blickensdorf M, et al. *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.

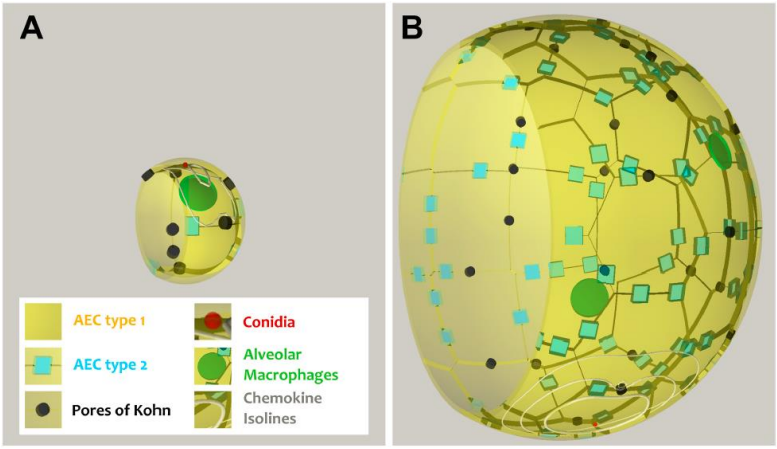


Figure 3: Visualization of a to-scale alveolus in the hybrid agent-based model for mouse (A) and human (B).

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3. Third party funding

AutoScreen (European Regional Development Fund and the State of Thuringia, 2017-2020)

Balance of the Microverse (Excellence Cluster of the DFG, first funding perdio 2019-2026)

FungiNet (Collaborative Research Center of the DFG, second funding period 2017-2021)

InfectoOptics (Leibniz ScienceCampus [Speaker: Marc Thilo Figge], second funding period 2019-2023)

PolyTarget (Collaborative Research Center of the DFG, first funding period 2017-2021)

Lehrstuhl für Biomolekulare Chemie

Prof. Dr. Christian Hertweck

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

1. Research

In microbial interactions bacteria employ diverse molecules with specific functions, such as sensing the environment, communication with other microbes or hosts, and conferring virulence.

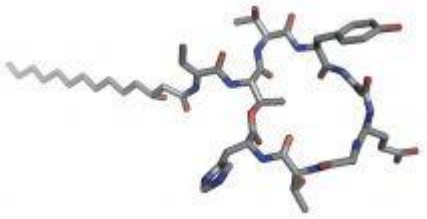
Most important results (Topics-Staff-Publications-News see also: https://www.leibniz-hki.de/en/biomolecular-chemistry.html)

Natural products play key roles as chemical mediators

In 2019, the Department Biomolecular Chemistry has discovered numerous natural products, and gained fundamental insight into their biosynthesis and functions. Most of the studies were performed in network programs such as ChemBioSys, InfectControl 2020, the JSMC, and the Microverse Cluster. *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).

Siderophores

Siderophores are key players in bacteria-host interactions, with the main function to provide soluble iron for their producers. We have unveiled two remarkable cases in which siderophores play unexpected, additional roles in microbial interactions. The first example involves human-pathogenic bacteria: 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). In the second example, a siderophore (gramibactin) from rhizosphere bacteria expands siderophore function beyond delivering iron to the host plant. Gramibactin features an unusual diazeniumdiolate moiety for iron chelation. By mutational analysis of the gene cluster, we identified genes necessary for diazeniumdiolate formation. Genome mining revealed a broad range of orthologous gene clusters in mainly plant-associated *Burkholderia*/*Paraburkholderia* species. Two new types of diazeniumdiolate siderophores, megapolibactins and plantaribactin were fully characterized. In vitro assays and in vivo monitoring experiments revealed 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).



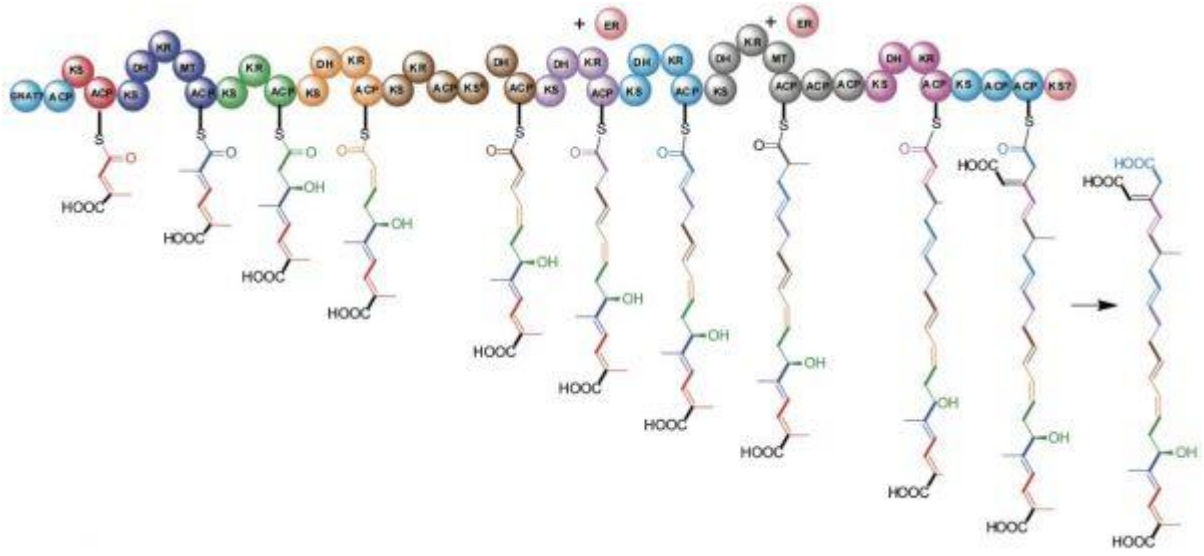
Using modern analytical methods, the structures of novel natural products from bacteria and fungi are elucidated. Structural diversity is increased by synthetic chemistry and biosynthetic approaches.

Hidden biosynthetic potential of anaerobic bacteria

We continued mining the hidden biosynthetic potential of anaerobic bacteria, which represent an underexplored source of bioactive natural products with unusual structural features. 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 pseudomonads. (*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. 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. In addition to prompting a revision of the CTA biosynthetic pathway, the reconstitution of CtaC provides the first example of a NRP thioamide synthetase. Finally, we used CtaC as a bioinformatic handle to demonstrate that thioamidated NRP biosynthetic gene clusters are more widespread than previously appreciated (Angew. Chem. Int. Ed. 2019d).

Assembly of polyketides

Recently, we also published a long-term project on the assembly of polyketides produced by modular type I polyketide synthases (PKSs). These complex natural produces play eminent roles in the development of medicines. Yet, the production of structural analogs by genetic engineering poses a major challenge. We succeeded in an evolution-guided morphing of modular PKSs inspired by natural recombination processes. By deletion and insertion of PKS modules we interconvert the assembly lines for related antibiotic and antifungal agents, aureothin (aur) and neoaureothin (nor) (aka spectinabilin), in both directions. Mutational and functional analyses of the polyketide-tailoring cytochrome P450 monooxygenases, and PKS phylogenies give contradictory clues on potential evolutionary scenarios (generalist-to-specialist enzyme evolution vs. most parsimonious ancestor). The KS-AT linker proves to be well suited as fusion site, which supports a model for alternative module boundaries in some PKS systems. This study teaches important lessons on the evolution of PKSs, which may guide future engineering approaches (*Nat. Commun.* 2019).



Using genetic and analytical tools, we also explore the hidden biosynthetic potential of yet neglected bacteria.

2. Publications

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.

Trottmann F, Franke J, Ishida K, Garcia-Altares M, Hertweck C (2019) A pair of bacterial siderophores releases and traps an intercellular signal molecule: An unusual case of natural nitrone bioconjugation. Angew Chem Int Ed 58, 200-204.

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, 13024-13029.

Schieferdecker S, Shabuer G, Knuepfer U, Hertweck C (2019) Clostrindolin is an antimycobacterial pyrone alkaloid from Clostridium beijerinckii. Org Biomol Chem 17, 6119-6121.

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

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3. Third party funding

DFG: SFB ChemBioSys Teilprojekt B01, *Chemische Mediatoren in komplexen Biosystemen,* Sonderforschungsbereich 1127/1, B01 und Teilprojekt Z01, SFB 1127/1, Z01

DFG: Leibniz Förderpreis/ Gottfried Wilhelm Leibniz Preis 2015, HE 3469/ 7-1

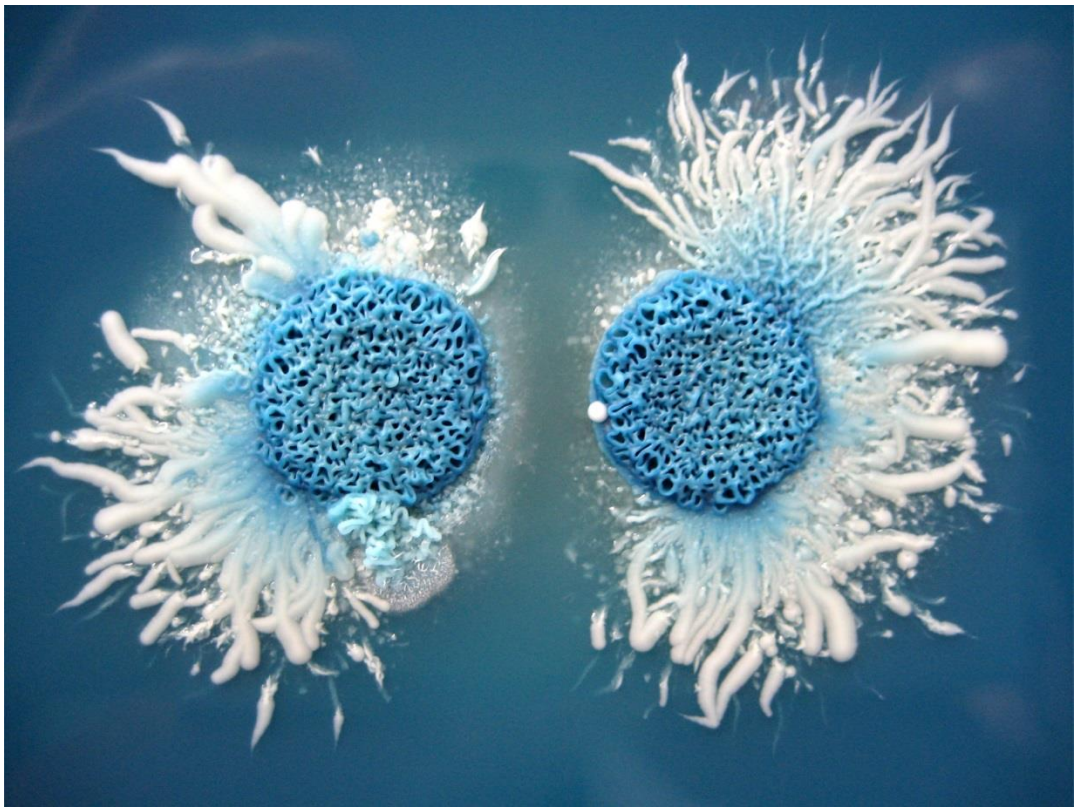
EU: H2020-Marie Sklodowska Curie Action (grant agreement number. 794343 — FUNBIOSIS — H2020-MSCA-IF-2017

Pakt Leibniz: *A Molecular Targeting Approach to Combat Human Pathogenic Fungi,* Projektnummer: K21712016

Pakt Leibniz: *Cystein-selective bioconjugation for next generation,* SAW-2018-FIYP-4-P5label

EFRE: Massnat, Hochauflösendes Massenspektrometer für die Entdeckung und Charakterisierung neuer Naturstoffe

Alexander von Humboldt Stiftung: *Biosynthesis of the secondary metabolite 6-thioguanine and its role in plant pathogenesis*, Ref 3.1 - USA - 1199295 - HFST-P



Lehrstuhl für Mikrobielle Pathogenität

Prof. Dr. Bernhard Hube

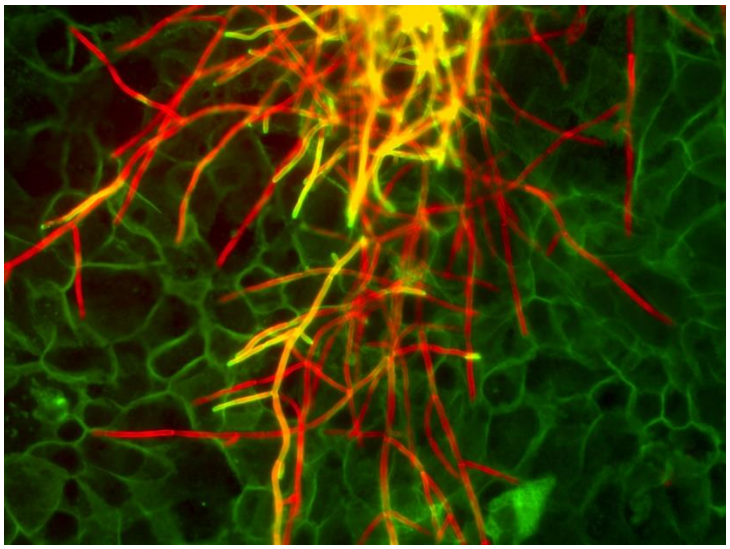
Leibniz Institute for Natural Product Research
and Infection Biology
Hans Knöll Institute

1. Research

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. For most important results (Topics-Staff-Publications-News see also: https://www.leibniz-hki.de/en/microbial-pathogenicity-mechanisms.html):

Role of a secreted peptide toxin – Candidalysin – in *Candida albicans* pathogenicity

Candida albicans pathogenicity has long been linked to its ability to form hyphae, and this morphological state has frequently been associated with infections ranging from superficial to systemic and even sepsis. What makes hyphae so important in pathogenicity, compared to the yeast morphological form, was, however, not completely understood: On the one hand hyphae are more adhesive and invasive on both biotic and abiotic surfaces, and this was often thought to sufficiently explain the different pathogenic potential of the two morphologies. But hyphae, or hyphae-associated processes, were also known to trigger an inflammatory response able to specifically sense pathogenic *C. albicans* — a "danger response" capable of discriminating between yeast and hyphal growth. To differentiate whether hyphae per se or hypha-associated factors are responsible for the "danger response", we performed, in collaboration with Prof. Julian Naglik and his team at the King's College in London (UK), a screening of a set of mutants that lack genes linked with filamentation. We evaluated markers of the "danger response", including the ability of the strains to cause damage to host cells. Of all the mutants tested, those that were unable to filament were consistently also unable to trigger the danger response, whereas all strains that were able to filament were fully able to do so – all except one. This strain lacks the ECE1 gene, which we later discovered to encode a peptide toxin that is secreted by invading hyphae and which we found to be critical for mucosal infection. Due to its ability to lyse host cells we named this toxin "Candidalysin", the first of its kind discovered in a human pathogenic fungus. "ECE1 and Candidalysin" have since become a major driving topic in our laboratory, putting us and our collaboration partners in a world-leading position in this new aspect of Candida pathogenity. In collaboration with Prof. Sarah Gaffen, University of Pittsburgh (USA), and other long standing collaborators, we have recently published another major finding on Candidalysin: We found that the innate immune response, which is predominantly orchestrated by IL-17 producing cells during *C. albicans* pathogenicity, is triggered by *C. albicans* hyphae more than by yeasts due to their Candidalysin secretion. While this was demonstrated in oral epithelial cells, other cell types are similarly affected by Candidalysin, including vaginal epithelia. This way the toxin exacerbates immunopathogenesis of C. albicans vaginitis, the most common manifestation of *C. albicans* infections.

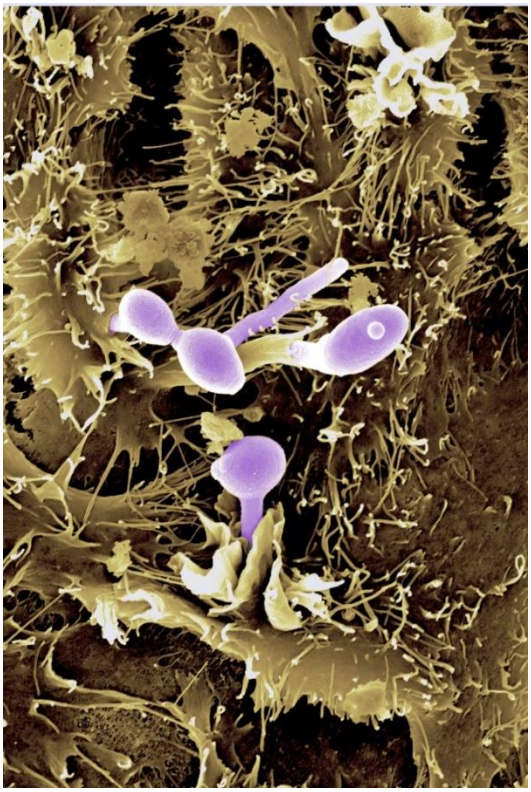


C. albicans hyphae invade into human epithelium (red hyphae) or grow on its surface (yellow hyphae). *Cover photograph - Eukaryotic Cell 2014 Aug;13(8) (Copyright © 2014, American Society for Microbiology)*

Networks of micronutrient acquisition during *Candida* infections

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

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



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

2. Publications (selected)

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

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

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Moyes DL, Wilson D, Richardson JP, Mogavero S, Tang SX, Wernecke J, Höfs S, Gratacap RL, Robbins J, Runglall M, Murciano C, Blagojevic M, Thavaraj S, Förster TM, Hebecker B, Kasper L, Vizcay G, Iancu SI, Kichik N, Häder A, Kurzai O, Luo T, Krüger T, Kniemeyer O, Cota E, Bader O, Wheeler RT, Gutsmann T, Hube B, Naglik JR (2016) Candidalysin is a fungal peptide toxin critical for mucosal infection. Nature 532, 64-68.

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

3. Third party funding

Deutsche Forschungsgemeinschaft (DFG) Collaborative Research Centre/Transregio 124 – FungiNet - Project C1 and Z2

DFG SPP 1580 Hu 528/17-1 and STA1147/1-1

Infect ERA-NET Program FunComPath; German Federal Ministry of Education and Health (BMBF) 031L0001A

The European Union, H2020–Marie Skłodowska-Curie Actions–European Training Networks–Marie Sklodowska-Curie (grant agreement no. 642095)–“OPATHY.”

Center for Sepsis Control and Care, Bundesministerium für Bildung und Forschung (BMBF) Grant Numbers 01E01002

Lehrstuhl für Mikrobielle Immunologie

Prof. Dr. Ilse Jacobsen

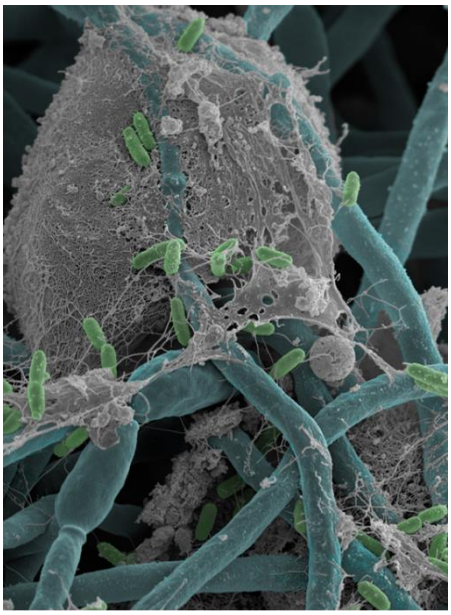
Leibniz Institute for Natural Product Research and Infection Biology
Hans Knöll Institute

1. Research

The Research Group Microbial Immunology investigates the pathogenesis of fungal infections, especially caused by *Candida albicans*, with a focus on interactions between the immune system and the host, and the consequences for development of disease. In mice, *C. albicans* infects almost all organs after intravenous application; however, while *C. albicans* is gradually cleared from liver and spleen, infection progresses in the kidneys. We aim to better understand the mechanisms of this organ-specific outcome, and to elucidate the exact role that filamentation plays in this. In parallel, we address the role of *C. albicans* as a commensal in the gut and the interactions with bacteria, especially in the context of factors that might facilitate translocation and development of life-threatening systemic infection. We believe that a deeper understanding on how infections develop and progress will allow to more accurately identify patients that benefit from prophylactic therapy and that it might lead to development of novel therapeutic approaches, aimed at strengthening host resilience or modulating fungal virulence. To this purpose, we have established a range of infection models, including mouse models, within out group and collaborate closely with other units at the HKI and groups from the FSU that work in the field of pathogenesis of *C. albicans* infections (MPM, Septomics HFI), immunology (IB, Prof. Jungnickel, Prof. Werz, PD Dr. Kosan), and bioinformatic analysis of –omics and image data (ASB, SBB, NM).

Although the organ-specific outcome of *C. albicans* infection in mice has been known for decades, the underlying mechanisms are only poorly understood. By performing gene expression profiling of the fungus and the host tissue during *in vivo* infection of mice, we identified distinct responses of both the host and the fungus in kidneys compared to the liver (*Sci Rep* 2016). The results indicate a delayed immune response accompanied by unhindered growth of the fungus in the kidneys. In contrast, proinflammatory responses occurred early in the liver and a fungal response suggesting interaction with phagocytes which likely mediates fungal control in the liver. Notably, hypha-associated genes were upregulated in the absence of visible filamentation in the liver, indicating an uncoupling of gene expression and morphology. We hypothesize that early interaction with resident phagocytes in the liver is mediating suppression of filamentation, which we are currently investigating in collaboration with PD Dr. A. Mosig (UKJ) using an organ-on-chip model that facilitates tissue-specific differentiation of macrophages. In a related project, we investigated the susceptibility and response of organ-specific epithelial cells (renal, hepatic, oral) to *C. albicans* infection. We found that both susceptibility and host response differed significantly between these epithelial cells in dependence of the fungal cell wall structure (Pawlik et al., in preparation), indicating that epithelial cells likely contribute to organ-specific interactions by distinct cytokine production profiles stimulating different downstream immune reactions.

Morphogenesis, and especially the ability to form hyphae, is considered a key virulence attribute of *C. albicans*. Surprisingly though, we found *C. albicans* mutants lacking *EED1*, a gene required for hyphal maintenance, to be fully virulent in a murine model of systemic candidiasis despite the absence of hyphae in infected tissue (Dunker et al., in preparation). We discovered that *EED1* reduces sensitivity to the filament-inhibitory effect of farnesol, a quorum sensing molecule. In addition, *EED1* regulates farnesol production and the hyphal maintenance-defect in the *eed1*Δ mutant strain is at least partially linked to farnesol (*Mol Microbiol* 2017). Using a genetic approach, we could show that *EED1* acts independently of other pathways previously implicated in farnesol sensing. These molecular findings raise novel questions concerning farnesol sensing and regulation of production (reviewed in *Curr Genet* 2017). Farnesol is however not only the major quorum sensing molecule of *C. albicans* but also involved in virulence (reviewed in *Crit Rev Microbiol 2017), providing possible link between* the quorum sensing and virulence phenotype of the *eed1*Δ mutant which we plan to address in the future.



4 k magnification

Electron micrograph depicting physical interactions of *Candida albicans* and *Proteus mirabilis* [Joanna M. Niemiec, Sandor Nietzsche, Susanne Linde].

The intestinal tract is the main reservoir of *C. albicans* and a source for infections. Using murine models we could show that *C. albicans* behaves as a commensal in this niche and does not trigger inflammatory responses even in a dysbiotic setting (Rudolphi et al., in preparation). This is likely to be influenced by interactions with bacterial members of the gut microbiota (reviewed in *Reference Module in Life Sciences* 2017 and *Current Topics Microbiol Immunol* 2018). We have found that such interactions influence bacterial virulence *in vitro* and are currently analysing whether this is also the case *in vivo*. Furthermore, we could demonstrate that alterations of oxygen levels in intestinal tissue, for example during hypoxic shock and reperfusion, affect the interaction of *C. albicans* with enterocytes, which might contribute to translocation in specific situations (Engert et al., in preparation).

Finally, we supported collaboration partners by providing our specific expertise in murine infection models and thereby contributed to a better understanding of the pathogenesis infections with *C. glabrata* (*Cell Microbiol* 2018), mucormycoses (*Virulence* 2017), and invasive aspergillosis (*Cell Chem Biol* 2016, *PLOS Path* 2016, *Mol Microbiol* 2016, *J Allergy Clin Immunol* 2017).

We envisage continuing our focus on organ-specific host-fungal interactions and the role of farnesol in pathogenesis, as well as further elucidating the impact of bacterial-fungal interactions on (i) *Candida* colonization and infection, and (ii) the consequences for the host's immune response and pathogenesis. The latter will include both analysis of interactions between distinct bacterial species and *C. albicans* and investigation and functional analysis of the microbiota in the context of colonization, dissemination, and the outcome of systemic infection. Interactions between microbes and the microbiome are receiving increasing attention across different areas of research as important determinants for disease development. This research focus furthermore is in line with the scope of the Jena School for Microbial Communication and the recently approved excellence cluster "Balance of the Microverse". Furthermore, a project addressing the impact of microbiota composition and *Candida* colonization on subsequent infections has recently acquired funding as part of the European ITN FunHoMics. We have established collaborations that enable us to perform state-of-the-art microbiome analysis (SBB and Prof. Slevogt, UKJ) which together with our expertise in murine models of colonization and infection should allow us to perform cutting edge research in this rapidly growing field.

2. Publications

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(5), 546-558.

Jacobsen ID (2019) Animal models to study mucormycosis. *J Fungi (Basel)* 5(2), 27. (Review)

Klaile E, Müller MM, Zubiría-Barrera C, Brehme S, Klassert TE, Stock M, Durotin A, Nguyen TD, Feer S, Singer BB, Zipfel PF, Rudolphi S, Jacobsen ID, Slevogt H (2019) Unaltered fungal burden and ethality in human CEACAM1-transgenic mice during *Candida albicans* dissemination and systemic infection. *Front Microbiol* 10, 2703.

Kresinsky A, Schnöder TM, Jacobsen ID, Rauner M, Hofbauer LC, Ast V, König R, Hoffmann B, Svensson C-M, Figge MT, Hilger I, Heidel FH, Böhmer FD, Müller JP (2019) Lack of CD45 in FLT3-ITD mice results in a myeloproliferative phenotype, cortical porosity, and ectopic bone formation. *Oncogene* 38(24), 4773-4787.

Krüger W, Vielreicher S, Kapitan M, Jacobsen ID, Niemiec MJ (2019) Fungal-bacterial interactions in health and disease. *Pathogens* 8(2), 70.

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.

3. Third party funding

EU: MARIE SKŁODOWSKA-CURIE ACTIONS Innovative Training Network (ITN) FunHoMic (2019-2023): Impact of microbiota diversity and *Candida* colonization on systemic candidiasis

BMBF: Center for Sepsis Control & Care, CSCC 2.0 (2018-2020): Applying an organ-on-chip model to elucidate principles of microbiome-host interactions

DFG: SFB/TR 124 FungiNet Pathogenic fungi and their human host (2013-2021): Networks of interaction; Project C5: Influence of gut microbiota on *Candida albicans* colonisation, host immune response and candidiasis

BMBF: InfectControl 2020, project „Management von Pilzinfektionen bei zunehmender Azolresistenz (FINAR; 2015-2018); in collaboration with O. Kurzai

BMBF: Center for Sepsis Control & Care, CSCC 2.0 (2015-2018): CanBac – Interaction of *C. albicans* with bacteria

BMBF: Forschungscampus InfectoGnostics: Innovative Diagnostik für Pneumonien bei Immunsuppression (2015-2020) – Teilvorhaben: Tiermodell opportunistische Erreger bei Pneumonien

Bio Pilot Plant

Chair of Synthetic Biotechnology

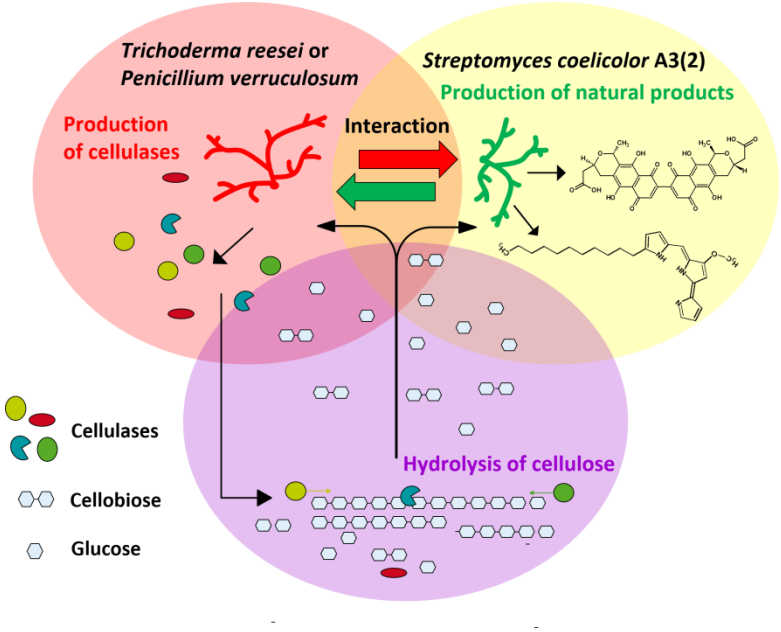
Prof. Miriam Agler-Rosenbaum

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

1. Research

The extensive laboratory remodeling of the Bio Pilot Plant labs, which was started in 2018, was concluded in the first quarter of 2019. With that doors were open to start realizing the new research agenda of the Bio Pilot Plant with the three focus areas 1) Bioprocess Development, 2) Microbial electrophysiology and 3) Droplet microfluidics.

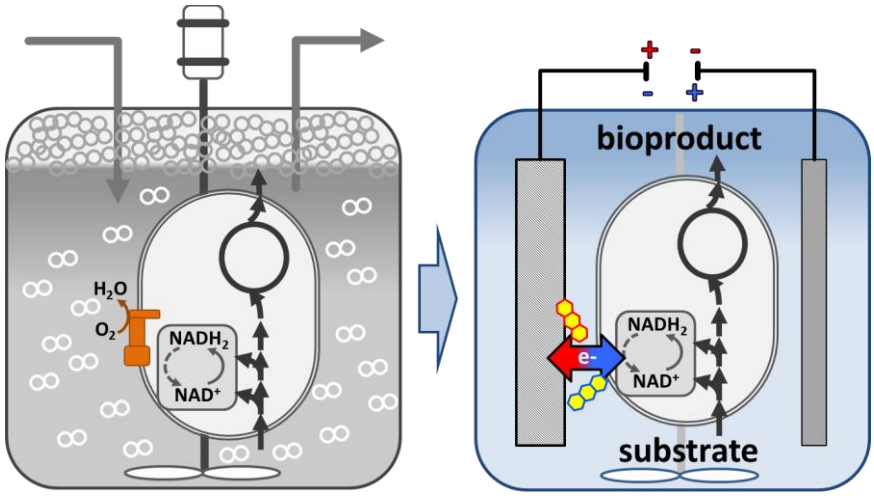
New research projects in the focus area of Bioprocess Development include fundamental research in cultivating amoeba in lab and pilot scale reactor systems (with Hillmann group), the formation of mycofactocin for structural anlysis (with Lackner group), bioctalytic formation of Psilocybin (with Hoffmeister group), spirocompounds formation by Actinomadura sp. (with Beemelmanns group), the characterization of cyclic lipopeptide productions (with Stallforth group) and controlled biotechnological processes with defined microbial co-cultures. 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 Priorty Programm “InterZell”.



Synthetic microbial consortia have been studied envisaging their application in the production of biofuels, organic acids and others. One of the aims is to use them in consolidated bioprocessing – CBP. In this work, we propose the use of two cellulolytic fungi, and one model filamentous bacterium biosynthesizing actinorhodin (ACT) and undecylprodigiosin (UP) for CBP starting from cellulose.

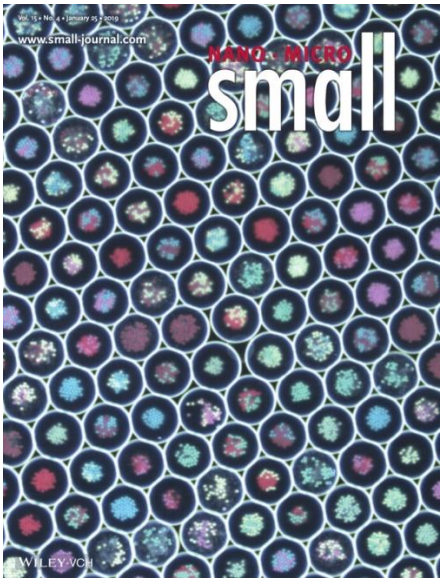
Further, Lars Regestein secured the funding for a research group to perform innovative pressure fermentations (700.000 €, Thüringer Aufbaubank) for challenging new bioprocesses. Specifically, the new team will utilize the new pressure reactor cascade for the formation of natural products with biochemically difficult microbial systems, which are very viscous, tend to strong foam formation and strong catabolic repression. Moreover, anaerobic and anoxic CO2-consuming bioprocesses will be also in the focus of the new sub-group. The new research team will start up in July 2020.

With the opening of the new laboratories, the establishment of Microbial Electrophysiology as a new research area has started. 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; and ii) we investigate, engineer and utilize CO2-fixing bacteria for new bioelectrochemical productions. 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 in December 2019. Thus, this research area will be strongly extended in 2020 with the hiring of four new group members.



The newly awarded e-MICROBe ERC consolidator grant will develop physiological pathways to turn aerobic biotech processes into electro-respiration processes during the next years.

The highlight of the Droplet Microfluidic Research sub-group is a publication in the journal "Small", - 2019 Medac 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). 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 (CoE Microverse – one Postdoc, LSC InfectoOptics, VersaDrop – one PhD student), the research capacity of this team was sustained. In future only one PhD student will focus his research on the technical advancement of the microfluidic platform, while all group members work with local PIs to employ and exploit the platform for very different scientific microbial questions. Collaborations have been started with A. Brakhage, H. Kries, K. Küsel, K.-U. Totsche.



The cover of SMALL showing picoliter droplets whose content is encoded by colored polysterene beeds.

As a core strategy, these biological questions will still be complemented by engineers/physicists within the group and from collaborating partners like IPHT and IOF to further expand on the possibilities of the platform regarding function analysis and droplet handling.

2. Publications

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3. Third party funding

Collaborative project – “Microfluidic platform technology for ultra-high-throughput screening of novel antimicrobial compounds from microorganisms - DropCode”, funded by the Free State of Thuringia.

Fiber based analysis of microorganisms in picoliter droplets, sub-project in the InfectoOptics Campus, funded by Life Science Foundation and Leibniz Foundation.

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

Innovative microbial sources for new antiinfectives, funded by German Center for Infection Research (DZIF).

Sub-project in SPP “Novel production processes and multi-scale analysis, modelling and design of cell-cell and cell-bioreactor interactions (InterZell)” funded by the DFG.

Sub-project in Balance of the Microverse, Cluster of Excellence funded by the DFG.

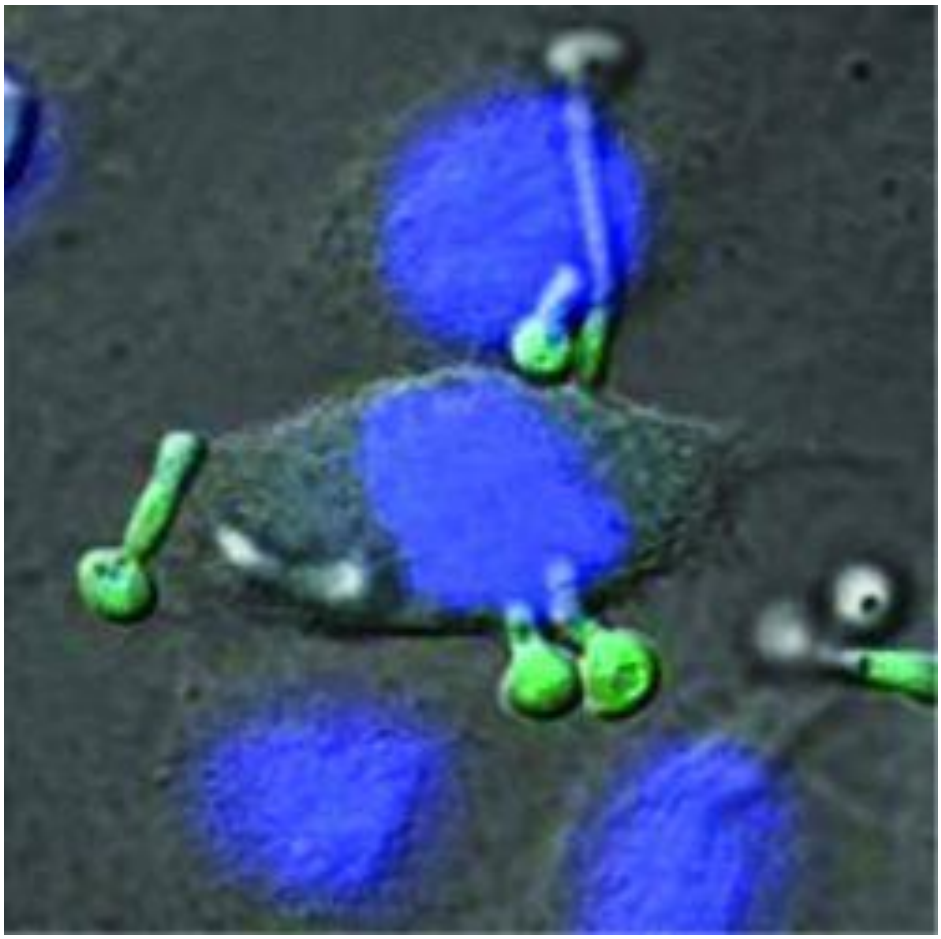
4. Successfully completed theses

Seraphine Jochem. Etablierung einer anaeroben Mischkultur aus Clostridium autoethanogenum und Clostridium kluyveri. FSU Jena, B. Sc. Biochemistry/Molecular biology

Leon Katzengruber. Method development for gas analysis of fermentation processes and fatty acid biomarker analysis on a gas chromatograph. FSU Jena, B. Sc. Biochemistry/Molecular biology

Seo Kyoyoung. Optimization of the fermentation process for production of the antibiotic jagaricin. FSU Jena, M. Sc. Microbiology

Carl Telle. Veterinärarzneimittel in Wirschaftsdüngern – Entwicklung einer angepassten Analytik und Untersuchung von Wirkstoffreduktion. FSU Jena, Biomaterialien und Medizintechnik



Lehrstuhl für Infektionsbiologie

Prof. Peter Zipfel

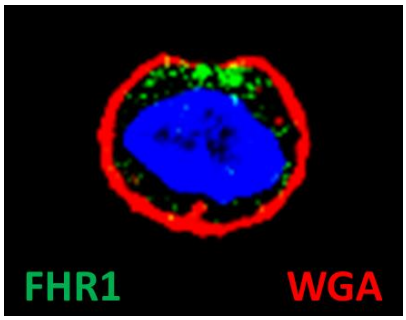
Leibniz-Institut für Naturstoff-Forschung
und Infektionsbiologie
Hans-Knöll-Institut

1. Research

The Department of Infection Biology is located at the Leibniz Institute for Nautral Product Research and Infection Biology, Hans Knöll Institute. Our work concentrates on the role of complement a central part of innate immunity, in infection, inflammation and human diseases. In evolution complement exists 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.

Microbial immune evasion

The role of fungal and microbial immune escape proteins, with focus on multifunctional microbial moonlighting proteins was analyzed in *C. albicans* (*Mol Immunol* 2017) and *A. fumigatus* (*Front Immunol* 2018), for the pathogenic bacteria *Borrelia bavarensis, Streptococcus pneumoniae* (*Sci Rep* 2017, *J Inf Dis* 2018) and for the multicellular parasite *Plasmodium falciparum* (*J Immunol* 2019). 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 (*Mol Immunol* 2017). Based on their multitude of action, these proteins have additional roles and also modulate the cellular immune response (*mBio* 2017*, Frontiers Microbiol* 2017).



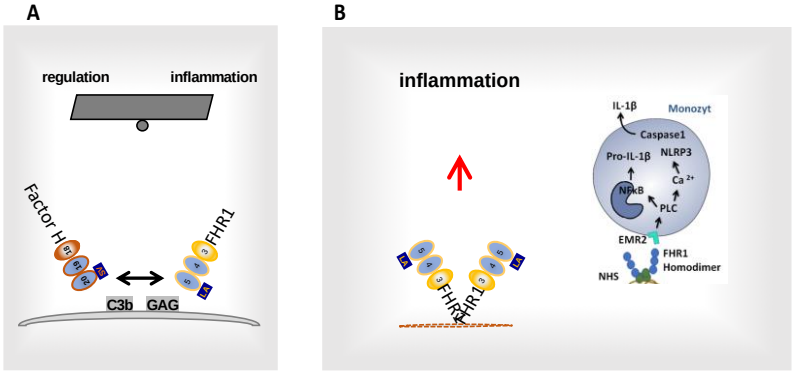
FHR1 binds to sites of membrane damage. Necrotic human monocytes when stained with FHR1 (green fluorescence) and WGA (wheat germ agglutinin; red fluorescence) demonstrates FHR1 binding at sites of membrane damage. FHR1 binds to sites where the cellular membrane is ruptured. One ligand formed at such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

The role of complement proteins in particular of Factor H related proteins (FHRs) in human kidney diseases was evaluated (*Nature Rev Nephrol* 2019). Laminis, like laminin 521 which are exposed in the damaged kidney were identified as new binding ligands of FHR5 (*J Immunol* 2018). Based on the characterization of a new gene variants and new forms of autoantibodies (*Kidney Int* 2019) 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 (*J Am Soc of Nephrology* 2018, *J Am Soc of Nephrology* 2017). A new function of the Factor H related

protein1 (FHR1) as activator of the monocytic inflammasome at necrotic sites of vasculopathies was identified (*Nature Communications* 2019)(Figure 2).

Complement activating enzymes

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 of 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.



FHR1 has dual immunomodulatory roles. (A) FHR1 with the C-terminal region competes with Factor 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

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* deficient and autoimmune positive 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 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 (*Nature Medicine* 2019).

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 yeasts *C. albicans* and *A. fumigatus* demonstrates the complexity of specific fungal immune evasion proteins, furthermore characterizes the sophisticated mechanisms that pathogenic microbes use to control host the immune attack and to survive in an immunocompetent host. The related binding profiles and overlapping functions of such pathogen proteins reveals common themes of immune evasion, describes strategies for immune evasion of microbial pathogens and identifies 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 infections 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 underling genes and of autoimmune factors can deregulate this delicate immune homeostasis and in consequence can result in human diseases and in autoimmunity.

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Patent applications 2019

Zipfel PF, Wiech T, Person F, Wulf S (2019) C3/C5 convertase assays. EP19189415. Priority: 31.07.2019

3. Third party funding

DFG	CRC FungiNet	TP C06
	CRC with University Hospital Eppendorf, Hamburg	SFB 1192/2 Project B4, Immune Mediated Glomerular Diseases
	DFG Prof. Zipfel	
IRLS	Immune evasion of *Streptococcus pneumoniae*	
DAAD	PhD project Shanshan Du	
Others	Kidneeds Grant	

4. Team

Mitarbeiter*innen der Forschungsstelle für Gartenbauliche Kulturpflanzen

Lehrstuhl für Molekulare Phytopathologie

Prof. Dr. Philipp Franken

Am 1. Januar 2019 ist in Erfurt-Kühnhausen die Forschungsstelle für Gartenbauliche Kulturpflanzen (FGK) unter der wissenschaftlichen Leitung von Philipp Franken an den Start gegangen. Der Betrieb dieser Einrichtung wird durch Projektmittel des Bundes und des Freistaats Thüringen gewährleistet. Die Forschungsstelle ist administrativ in die Fachhochschule Erfurt eingegliedert, wissenschaftlich aber durch einen Kooperationsvertrag eng mit der Friedrich-Schiller-Universität verbunden. Das Jahr 2019 war vor allem durch die Besetzung der 27 Stellen in den vier Forschungsgruppen, in der Verwaltungseinheit und in der Infrastruktureinheit und durch die Etablierung von Strukturen und Prozessen zum Betrieb einer wissenschaftlichen Einrichtung geprägt. Im Folgenden wird über die Arbeiten in der Forschungsgruppe „Pflanzen-Mikroorganismen Wechselwirkungen im nachhaltigen Anbau“ berichtet, wobei auch auf die noch laufenden Projekte am Leibniz-Institut für Gemüse- und Zierpflanzenbau eingegangen wird. Informationen über die anderen Gruppen in der Forschungsstelle finden Sie unter www.fh-erfurt.de/FGK.

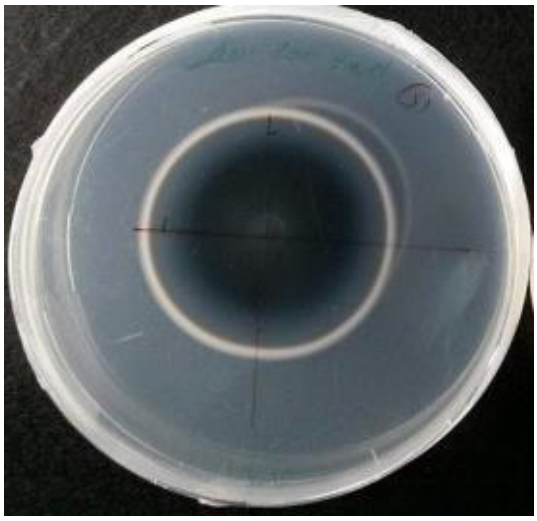
1. Forschung

Wurzelbesiedelnde Pilze: Funktion und Anwendung

Besiedelung einer Petunienwurzel mit dem arbuskulären Mykorrhizapilz *Rhizoglomus irregulare*

Die Wurzeln der höheren Landpflanzen sind von einer Vielzahl von Mikroorganismen besiedelt. Pilzliche Wurzelendophyten haben dabei die besondere Eigenschaft, durch ihr Netzwerk aus Hyphen die Umgebung der Wurzel mit den Zellen der Wurzelrinde und auch die Wurzeln verschiedener Pflanzen untereinander zu verbinden. So sorgen sie in terrestrischen Ökosystemen für den Austausch von Nährstoffen und Signalen. Durch ihre Wechselwirkungen mit der Pflanze können pilzliche Endophyten die Aufnahme von Nährstoffen, die Resistenz und Toleranz gegen biotischen und abiotischen Stress und die Qualität von Pflanzenprodukten fördern. Zu den meist verbreiteten Wurzelbesiedlern gehören die arbuskulären Mykorrhizapilze (Zygomycota), Pilze der Ordnung Sebacinales (Basidiomycota) und die sogenannten Dark Septate Endophytes (DSEs, Ascomycota).

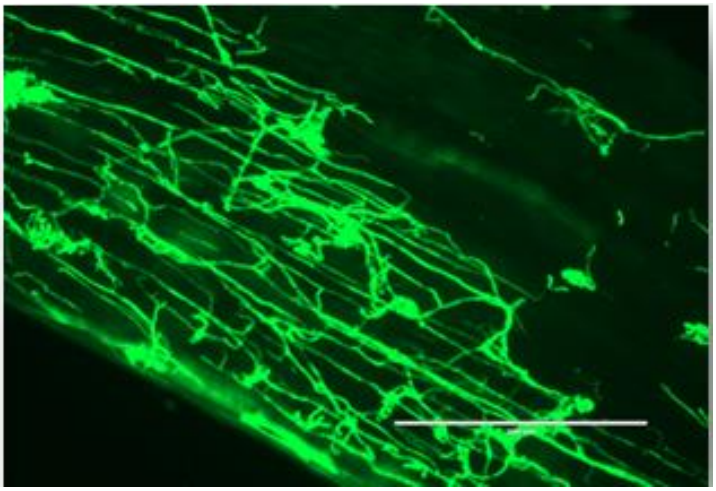
Eine wichtige Voraussetzung für die Förderung der Toleranz der Pflanzen gegenüber Trockenheit, erhöhte Salzgehalte oder Kontaminationen mit Schwermetallen ist die abiotischen Stresstoleranz der wurzelbesiedelnden Pilze selbst. DSEs sind durch die Einlagerung hoher Mengen an Melanin in ihren Hyphen charakterisiert und die Rolle des Melanins für die hohe Stresstoleranz der Pilze wurde oft diskutiert. Nach längerer Kultivierung unter hohen Salzgehalten wurde der Melaningehalt in den Hyphen zwar erhöht. Durch den Einsatz von Inhibitoren der Melaninbiosynthese und von Albinomutanten konnte aber gezeigt werden, dass das Melanin nicht zur Stresstoleranz der DSEs beiträgt (Dissertation Dalia Gaber, 2019).



Melaninbildung bei *Cadophora* sp.

Nachdem sich herausgestellt hatte, dass DSEs ähnlich weit verbreitet sind wie AM Pilze und Endophyten der Ordnung Sebacinales, wurde untersucht, in wie weit sie auch zur Pflanzenernährung und Pflanzengesundheit beitragen Dabei zeigte sich, dass diese Pilze in der

Lage sind, Phosphat aus verschiedenen organischen und anorganischen Quellen für die Pflanze verfügbar zu machen, dieses Phosphat aber nicht durch die Hyphen aus dem Boden in die Wurzel in signifikanten Mengen transportiert wird (Yakti et al. 2019a, 2019c). In einem *in vitro* experimentellen System konnte für den DSE *Cadophora sp.* antagonistische Eigenschaften gegen verschiedene bodenbürtige Pathogene der Tomate nachgewiesen werden. Diese antagonistischen Eigenschaften wurden bei Besiedelung der Pflanze allerdings herunterreguliert, genauso wie die Expression bestimmter Gene der Pflanzenverteidigung, so dass der DSE die Infektion der Pflanze mit den Pathogenen eher förderte (Yakti et al. 2019b).



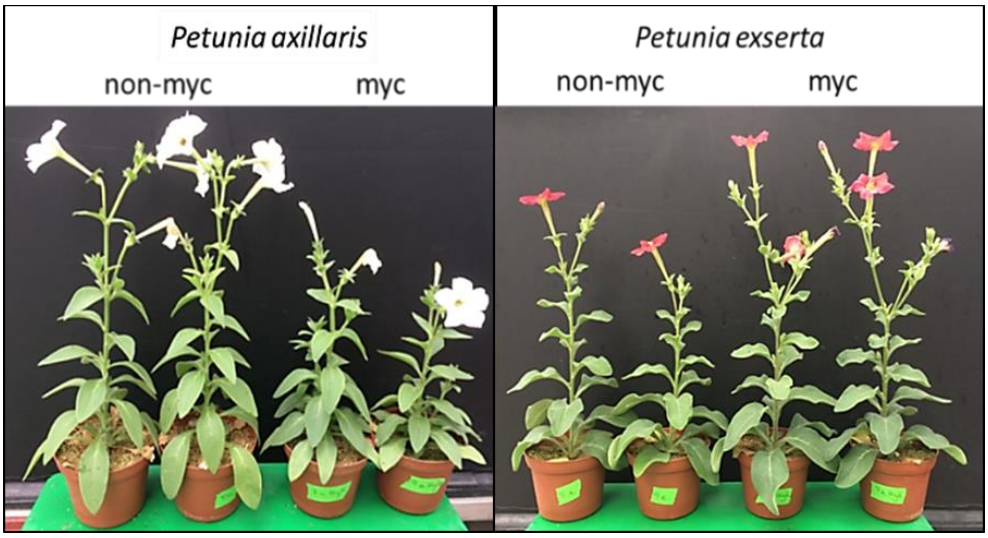
Besiedelung einer Tomatenwurzel mit dem DSE *Cadophora* sp.

Arbuskuläre Mykorrhizapilze können um die Wurzel herum einen erhebliche Teil der mikrobiellen Biomasse ausmachen. Man spricht in dem Zusammenhang von der sogenannten Mykorrhizosphäre. Dieses Hyphennetzwerk sorgt nicht nur für den Transport von Nährstoffen und Signalen, es beeinflusst auch die physikalischen und chemischen Eigenschaften des Bodens. Unter anderem wird die Wasserhaltekapazität verändert und diese Veränderung ist abhängig von der Größe der Bodenpartikel (Richard Pauwels, Masterarbeit 2019). Durch diesen Einfluss trägt der AM Pilz indirekt zur Wasserversorgung der Pflanze bei und erhöht so deren Trockentoleranz.

Identifizierung von Mykorrhiza-relevanten Pflanzengenen

Die Antwort der Pflanzen auf wurzelbesiedelnde Pilze ist neben den Umweltbedingungen und der Wahl des Inokulums auch vom pflanzlichen Genotyp abhängig. Deshalb müssen für zukünftige Züchtungsprogrammen von Kulturpflanzen molekulare Marker entwickelt werden, die voraussagen, ob der Einsatz der Pilze zu einer Erhöhung der Leistungen dieser Kulturpflanzen führt. Die Identifizierung der entsprechenden Gene kann zum einen zielgerichtet durch Hypothesen getrieben erfolgen. Zum anderen kann in segregierenden Populationen nach sogenannten Quantitative Trait Loci (QTLs) gesucht werden, deren Analyse dann zu der Identifizierung solcher Gene führt.

Ob die Besiedelung der Pflanze mit einem AM Pilz zu einer Erhöhung der Biomasse führt hängt auch davon ab, wie viele Ressourcen die Pflanze dem Pilz zur Verfügung stellt. In früheren Studien konnte gezeigt werden, dass dabei der Saccharose-Transporter SUT2 in der Tomate eine zentrale Rolle spielt. SUT2 ist an der Membran lokalisiert, die die pilzlichen Arbuskel, kleine Hyphenbäumchen im Apoplast der pflanzlichen Zelle, umgibt. Dort interagiert SUT2 in einem Proteinkomplex mit anderen Proteinen, unter anderem mit Enzymen der Biosynthese und Faktoren der Signaltransduktion für die Phytohormonklasse der Brassinosteroide. Das Membrane Steroid Binding Protein 1 in diesem Proteinkomplex kann solche Brassinosteroide binden und nimmt so positiven Einfluss auf die Biomasse der Pflanze und auf die Architektur der pilzlichen Arbuskel (Von Sivers et al. 2019).



Reaktion von Wildarten der Gattung Petunia auf Mykorrhizierung

Die Petunie ist nicht nur eine bedeutende Kulturpflanze, sondern wird auch als Modell in der Grundlagenforschung verwendet. In einem Konsortium, an dem auch Wissenschaftler*innen der FGK beteiligt sind, wurde in den letzten Jahren die Genome der Wildarten der Petunie sequenziert und verschiedene Werkzeuge zur funktionellen Genanalyse entwickelt. Interessanterweise reagieren diese Wildarten sehr unterschiedliche auf die Mykorrhizierung, Dies zeigten nähere Untersuchungen zur Besiedelung, zur Genexpression und in Zusammenarbeit mit dem MPI für Chemische Ökologie zur Akkumulierung des biochemischen Mykorrhizamarkers Blumenol. Eine Kreuzungspopulation mit rekombinanten Inzuchtslinien, die aus diesen beiden Wildarten hervorgeht, steht mit den entsprechenden Karten zur Verfügung und wird nun zur Identifizierung der QTLs für die Antwort auf die Mykorrhiza verwendet.

2. Publikationen

Druege U, Hilo A, Pérez-Pérez JM, Klopotek Y, Acosta M, Shahinnia F, Zerche S, Franken P, Hajirezaei M. 2019. Molecular and physiological control of adventitious rooting in cuttings: phytohormone action meets resource allocation. Ann Bot 123, 929–949.

Druege U, Klopotek Y, Zerche S, Hajirezaei MR, Yang H, Franken P. 2019. Efficient adventitious root formation in *Petunia hybrida* cuttings: when signals meet resources. Acta Horticulturae 1242: 917-925.

Franken P, Takken FLW, Rep M. 2019 Transcript accumulation in a trifold interaction gives insight into mechanisms of biocontrol. New Phytol 224, 547-549.

Von Sivers L, Jaspar H, Johst B, Roese M, Bitterlich M, Franken P, Kühn C. 2019. Brassinosteroids affect the symbiosis between the AM fungus *Rhizoglomus irregularis* and solanaceous host plants. Front Plant Sci 10, 571.

Yakti W, Kovács GM, Vági P, Franken P. 2019a. Impact of dark septate endophytes on tomato growth and nutrient uptake, Plant Ecol Divers 11, 637-648.

Yakti W, Kovács GM, Franken P. 2019b. Differential interaction of the dark septate endophyte *Cadophora* sp. and fungal pathogens *in vitro* and *in planta*. FEMS Microbiol Ecol 95, fiz164.

Yang H, Klopotek Y, Hajirezaei MR, Zerche S, Franken P, Druege U. 2019. Role of auxin homeostasis and response in nitrogen limitation and dark stimulation of adventitious root formation in petunia cuttings. Ann Bot 124, 1053–1066.

Yakti W, Andrade-Linares D, Ngwene B, Bitterlich M, Kovács G, Franken P. 2019c. Phosphate nutrition in root–fungus interactions. In: T. Hodkinson, F. Doohan, M. Saunders, B. Murphy (eds.) Endophytes for a Growing World. Cambridge University Press, Cambridge: pp 120-142.

Zhang H, Franken P. 2019. Truncated arbuscules formed in the *Medicago truncatula* mutant m*tha1* maintain mycorrhiza-induced resistance. In: F. de Bruijn (ed.) The Model Legume *Medicago truncatula* - 2 vol. John Wiley & Sons, Hoboken NJ: pp. 513–520.

3. Drittmittelprojekte

Projektträger	Vorhaben	Laufzeit	Mittel in 2019
TMWWDG	Pflanzen-Mikroorganismen Wechselwirkungen im nachhaltigen Anbau	01.01.2019-31.12.2023	817.677,00 €
EU Horizon 2020 research and innovation programme	BestPass: Boosting plant-endophyte stability, compatibility and performance across scales	01.08.2015 – 30.11.2019	52.261,00 € + 2 Doktoranden

4. Studium und Lehre

Angebotene Module der Mikrobiellen Kommunikation

Im Jahr 2019 wurde noch keine Lehre an der FSU angeboten.

Abschlussarbeiten (noch an der Humboldt-Universität zu Berlin)

Richard Pauwels: "Mycorrhizosphere effects: Substrate-specific shifts of water retention and hydraulic conductivity beyond the ambit of roots" (Juni 2019)

5. Wissenschaftlicher Nachwuchs

Promotionsabschlüsse (noch an der Humboldt-Universität zu Berlin)

Dalia Gaber: „Acclimatization of dark septate endophytes (DSEs) to abiotic stress and their role in improving plant tolerance" (Oktober 2019)

6. Gleichstellung und Familie

Anteil Frauen	Anteil Männer	Mit Kindern unter 12 Jahren
6	3	3

7. Internationales

Kooperationen mit internationalen Universitäten

Université de Lorraine – **Frankreich**

Eötvös Loránd University – **Ungarn**

University of Copenhagen – **Dänemark**

University of Amsterdam – **Niederlande**

Austrian Institute of Technology – **Österreich**

Institute for Sustainable Plant Protection, C.N.R.– **Italien**

Internationale Tagungsbesuche

World Petunia Days 2019, 03.09 – 06.09.2019, Mailand, Italien

miCROPe 2019: Microbe-assisted crop production – opportunities, challenges & needs, 02.12. – 05.12.2019, Wien, Österreich

CNR Symposium: Le frontiere della ricerca agroalimentare per la sosteni, 12.12. – 13.12.2019, Bologna, Italien

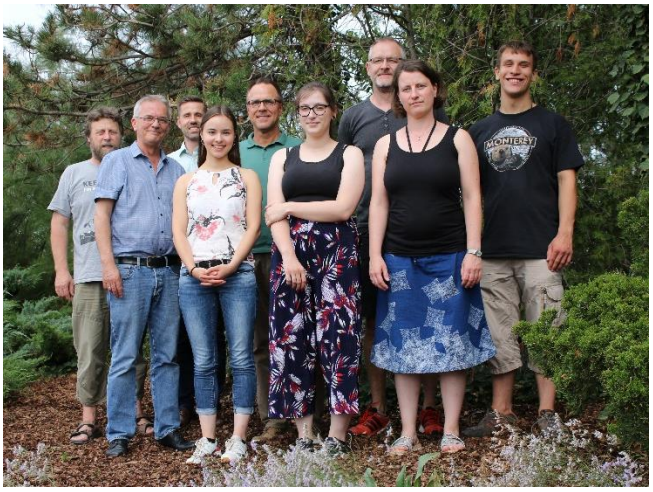
Internationale Gastwissenschaftler*innen

Mohammad Zarea, Ilam Universität, Iran, 03.07 – 30.09.2019

Rahma Azri, Technopole Borj Cedria, Tunesien, 01.10 – 31.12.2019

8. Organisierte Veranstaltungen

26th International Eucarpia Symposium Section Ornamentals: Editing Novelty, FH Erfurt, 01.09 – 04.09.2019, 110 Teilnehmer*innen



Eucarpia Symposium Organisationsteam der Forschungsstelle für Gartenbauliche Kulturpflanzen

9. Administration/Finanzen

Beschäftigungsstruktur

	Personen	Stellenanteile
Beschäftigte im Rahmen von Drittmitteln		
Wissenschaftliche Mitarbeiterinnen (davon eine Promovendin)	2	2,0
Technische Assistenz	2	2,0

10. Team

Wissenschaftlerin
Katja Burow
Technische Assistenz
Sabine Czekalla
Janett Grimmer
Promovierende
Julia Brandes
Vincenzo De Rocchis*
Dalia Gaber*
Shubhangi Sharma*
Studierende
Richard Pauwels*
Julius Dawydow
Marla Jeckstiess

*Am Leibniz-Institut für Gemüse- und Zierpflanzenbau tätig

Lehrstuhl für Microbiome Science

Prof. Dr. Christina Warinner)

HARVARD
Department of Anthropology

Max Planck Institute for the Science of Human History
Prof. Dr. Christina Warinner
Kahlaische Strasse 10
07745 Jena
GERMANY

1. Research

We study the long and complicated relationship between humans, their food, and their microbes. In doing so, we study not only the food cultures and microbiomes of people today but also the microscopic and biomolecular traces of foods and microbes that prehistoric peoples left behind - in dental calculus, paleofeces, and pottery residues: *an archaeology of the invisible*. We then combine this information with paleogenomic studies of prehistoric migrations and human genetic adaptations to build up a picture of our long and tangled dietary and microbial history.

This information can then be used to begin answering questions such as: *What does it mean for a human diet to be healthy or natural? Why does the oral microbiome causes disease in more than half the human population? Why is metabolic disease increasing so rapidly in industrialized societies? Why are some people lactose intolerant and others are not? Where do food microbes come from and are they beneficial? How did humans come to have one of the most diverse diets of any species on earth?*

The goal of our work is to understand how microbes have profoundly influenced our evolution and how they continue to shape and impact our health today through our microbiome, our food systems, and disease.

Main Focus

Ancestral human microbiome, origins of dairying, paleogenomics, proteomics, microbiology, archaeological science

Primary Projects:

Dairying and Dietary Adaptive Evolution in Prehistory

Origins of Dairying in Ancient Central Asia Project

Origins of Dairying in Ancient Europe Project

Heirloom Microbes

Uncovering Dietary Practices through the Proteomic Analysis of Ceramics

Evolution and Ecology of the Human Gut Microbiome

Evolution and Ecology of the Human Oral Microbiome

Ancient Nepal Population Genetics

2. Publications

Huebler R, Key FM, Warinner C, Bos KI, Krause J, Herbig A. (2019) HOPS: Automated detection and authentication of pathogen DNA in archaeological remains. Genome Biology 20:280. https://doi.org/10.1186/s13059-019-1903-0

Hernández-Hernández O, Hernández-Zaragoza DI, Barquera R, Warinner C, López Gil C, Arrieta-Bolaños E, Clayton S, Bravo-Acevedo A, Ramos-de la Cruz F, Méndez-Mani P, Pavón-Vargas M, Zúñiga J, Yunis EJ, Bekker-Méndez C, Granados J. (2019) Genetic diversity of HLA system in two populations from Oaxaca, Mexico: Oaxaca City and rural Oaxaca. Human Immunology, in press. DOI: 10.1016/j.humimm.2019.07.278.

Aronsen GP, Fehren-Schmitz L, Krigbaum J, Kamenov GD, Conlogue G, Warinner C, Ozga A†, Sankaranarayanan K, Griego A, DeLuca DW, Eckels HT, Byczkiewicz R, Grurich T, Pellatier N, Brownlee S, Marichal A, Williamson K, Tonoike Y, Bellantoni NF. (2019) The dead shall be raised: Multidisciplinary analysis of 19th century human skeletons reveals complexity in New Haven Connecticut immigrant socioeconomic history and identity. PLoS ONE 14(9): e0219279. DOI: 10.1371/journal.pone.0219279

Geber J, Tromp M, Scott A†, Bouwman A, Nanni P, Grossmann J, Hendy J, Warinner C. (2019) Relief food subsistence revealed by microparticle and proteomics analyses of dental calculus from victims of the Great Irish Famine. Proceedings of the National Academy of Sciences USA 201908839. DOI: 10.1073/pnas.1908839116.

Velsko IM†, Fellows-Yates JA†, Aron F, Hagen RW, Frantz LAF, Loe L, Rodriguez Martinez JB, Chaves E, Gosden C, Larson G, Warinner C*. (2019) Microbial differences between dental plaque and historic dental calculus are related to oral biofilm maturation stage. Microbiome 7:102. DOI: 10.1186/s40168-019-0717-3

Hofman CA, Warinner C*. (2019) Ancient DNA 101: An introductory guide in the era of high-throughput sequencing. SAA Record 19(1):18-25.

Radini A, Tromp M, Beach A, Tong E, Speller C, McCormick M, Dudgeon JV, Collins MJ, Rühli F, Kröger R, Warinner C*. (2019) Medieval women's early involvement in manuscript production suggested by lapis lazuli identification in dental calculus. Science Advances 5, eaau7126. DOI: 10.1126/sciadv.aau7126.

Prof. Dr. Gabriele Diekert

Ehemalige Professorin des Lehrstuhls für Angewandte und Ökologische Mikrobiologie.

Deutsche Forschungsgemeinschaft

Lebenswissenschaften 2:
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Institut für Mikrobiologie
Lehrstuhl für Angewandte und Ökologische Mikrobiologie
Philosophenweg 12
07743 Jena

GZ: FOR 1530/2

09.06.2020 Eig

Forschungsgruppe: Anaerobic Biological Dehalogenation: Organisms, Biochemistry, and (Eco-)physiology (FOR 1530)

Sehr geehrte Frau Professorin Diekert,

der von Ihnen eingereichte Abschlussbericht wurde in der Zwischenzeit begutachtet und hat Zustimmung gefunden.

Im Folgenden übermittle ich Ihnen Kommentare und Hinweise aus der Begutachtung:

Gutachten 1:
„Die Forschungsgruppe FOR1530 wurde im Jahr 2011 ins Leben gerufen als ein Zusammenschluss von Mikrobiologen aus dem Raum Jena-Halle-Leipzig. Das Thema der Forschungsgruppe geht zurück auf jahrelange Vorarbeiten, insbesondere in den Arbeitsgruppen von Prof. Gabriele Diekert (Jena), Dr. Utel Lechner (Halle), sowie Dr. Lorenz Adrian und Dr. Ivonne Nijenhuis (UFZ Leipzig). Diese Mikrobiologen beschäftigten sich mit der Frage, ob die extrem schwerwiegenden chemischen Belastungen in den Böden des mitteldeutschen Chemiedreiecks (Bitterfeld-Halle) durch mikrobielle Aktivitäten abbaubar sind. Dabei isolierten sie Bakterienstämme, die halogeneirte organische Verbindungen unter anaeroben Bedingungen abbauen konnten, die *organohalide respiring bacteria* (OHRB). Allerdings sind diese Mikroorganismen extrem schwer zu kultivieren, sie verfügen über eine äußerst komplexe, bis dato

unterstandene Biochemie und genetische Systeme standen ebenfalls nicht zur Verfügung. Lange Zeit erschien es nahezu unlösbar, detaillierte molekulare Einblicke in diese organismengruppe zu erhalten und die Mechanismen der Dehalogenierungsreationen zu verstehen.
Es war daher konsequent, diese schwierige Aufgabe in einem multidisziplinären Team zu erforschen. Frau Diekert hat es geschafft, eine schlagkräftige Forschungsgruppe zu etablieren, die diese Herausforderung angenommen, und letztlich mit Bravour gemeistert hat. Die Arbeitsgruppe von Prof. Diekert fungierte dabei als ein Kondensationspunkt der Arbeiten in allen 7 Gruppen.

a) Wurden die im Antrag formulierten Forschungsziele erreicht?
Jeder der sieben Gruppen hat in ihrem jeweiligem Gebiet sehr erfolgreich gearbeitet. Der Mehrwert des Zusammenschlusses diverser molekularbiologischer Expertisen mit Methoden der öko- und molekularen Physiologie und Genetik zahlte sich insbesondere in der zweiten Fördereriode aus. Es erschienen überragende Publikationen zu diesem Thema. Die wichtigsten molekularen Mechanismen der anaeroben Atmungskettenreaktionen, bei denen Halogen-Atome abgespalten werden, konnte bis ins Detail geklärt werden. Ein Highlight ist sicherlich die *Science* erschienene Arbeit „Structural basis for organohalide respiration" aus der AG Diekert, sowie weitere hochrangig publizierte Arbeiten, u.a. in Nature Communications, AEM oder FEBS Journal. In der Begutachtung der ersten Förderperiode wurde von den Gutachtern noch angemerkt: *Insgesamt werden die Ergebnisse aus der vergangenen Förderperiode sehr positiv eingeschätzt, allerdings kann dies zum jetzigen Zeitpunkt zwar zufriedenstellend, aber nicht herausragend durch Publikationen belegt werden.*
Die Gutachter konnten jedoch bereits zu diesem Zeitpunkt absehen, dass der große Durchbruch in der zweiten Periode zu erwarten ist, was dann auch eingetreten ist. Es zeigt sich hier exemplarisch, dass man für große Ziele Durchhaltevermögen und Geduld benötigt. Beides ist in dieser Forschungsgruppe der Fall gewesen. Die gesteckten Ziele wurden erreicht, teilweise sogar deutlich übertroffen.

b) Welcher wissenschaftliche Zugewinn wurde durch den Verbund erzielt? Wurden strukturelle Maßnahmen ergriffen, durch die die Zusammenarbeit gestaltet und der Verbund gestärkt?
Die räumliche Nähe der Standorte Jana, Halle und Leipzig war sicherlich eine große Hilfe für die Etablierung einer eng verwobenen Zusammenarbeit. Die Arbeitsgruppen haben sich mehrmals jährlich zu intensiven Arbeitstreffen zusammengefunden. Zu Beginn des Projektes war Prof. Boll noch an der Uni Leipzig, aber auch nachdem er den Ruf auf die W3 Professur in Freiburg angenommen hat, bliebe er eng mit den anderen Gruppen verbunden. Diese intensive Zusammenarbeit war einer der Gründe für den großen Erfolg der Forschungsgruppe. Diese Ergebnisse wären durch die unkoordinierte Aktivität einzelner Gruppen, selbst bei gleichem oder sogar höherem Förderumfang,

nicht erzielt worden. Spezielle Module der Förderung (Fellow Programm oder ähnliches) wurde nicht in Anspruch genommen.

c) In welcher Form fand eine thematische oder örtliche Schwerpunktsetzung statt?
Die einzelnen Arbeitsgruppen hatten bereits zum Teil langjährige Erfahrung in der Erforschung des mikrobiellen Schadstoff-Abbaus. Der Zusammenschluss zur Forschergruppe erforderte also keine Umorientierung von laufenden Aktivitäten. Vielmehr führte er zu einer Verstärkung von ohnehin vorhandenen Expertisen, hin zu einem weltweit führenden Kompetenz-Netzwerk. Alle Arbeitsgruppen steigerten durch die Forschungsgruppe ihre Reputation und Produktivität, aber insbesondere die Arbeitsgruppe der Sprecherin Diekert erreichte dadurch gegen Ende ihrer Karriere einen fulminanten Höhepunkt.

d) Wie schätzen Sie die internationale Sichtbarkeit der Forschungsgruppe ein?
Die Forschungsgruppe organisierte zwei Internationale Konferenzen zu Thema Abbau halogenierte organischer Verbindungen (DehaloConI und DehaloCon II), bei denen führende ForscherInnen auf diesem Gebiet aus USA, Kanada, Australien, der Schweiz und Italien eingeladen waren. Es waren die ersten internationalen Tagungen zu dieser Thematik und es ist nach Ablauf der Forschungsgruppe eine Fortführung der Tagungsserie geplant (DehaloCon III im Jahr 2020 in Rom). Bei den vergangenen Tagungen wurden wichtige Kontakte geknüpft und neue Kollaborationen initiiert. Prof. Elisabeth Edwards (University Toronto) würdigt die Bedeutung dieser Treffen und den Beitrag der Forschungsgruppe zu den rasanten wissenschaftlichen Fortschritten in dieser Thematik.

e) Durch welche Maßnahmen wurde der wissenschaftliche Nachwuchs gefördert?
Mit Ivonne Nijenhuis, Nico Jehmlich und Jana Seifert waren von Anfang an 3 Nachwuchswissenschaftler in der Forschungsgruppe involviert. Nicht zuletzt dank der Förderung durch das FPR1530 Programm erhielt Frau Seifert einen Ruf an die Universität Stuttgart Hohenheim, zunächst als Junior-Professorin, seit 2019 W3. Frau Nijenhuis und Herr Jehmlich erhielten Festanstellungen als Gruppenleiter am UFZ Leipzig. Mit Ivonne Nijenhuis und Torsten Schubert konnten zwei Nachwuchswissenschaftler ihre Habilitation erreichen. Weiterhin wurden die Doktoranden, die in FOR1530 mitgearbeitet haben, sehr stark gefördert und gefordert. So waren die Doktoranden eng in die Organisation der diversen FOR Konferenzen eingebunden. Darüber hinaus erhielten sie im Rahmen der Forschungsgruppe einen weiten intellektuellen *input* und lernten von Anfang an den Wert der engen Kooperation von Experten zu schätzen.

f) Welche Maßnahmen zur Gleichstellung von Wissenschaftlerinnen und Wissenschaftlern wurden umgesetzt?
In der Forschungsgruppe herrschte von Anfang an *gender equality,* da vier Pis weiblich waren (Diekert, Lechner, Nijenhuis und Seifert), und auch die Mehrheit der Doktoranden und Doktorandinnen war weiblich. Spezielle Module zur Förderung des weiblichen Nachwuchses wurden daher offenbar nicht in Anspruch genommen, zumindest sind dem Gutachter keine solchen Maßnahmen bekannt.

g) Transferaspekte: Wurden aus Anwendungssicht Fortschritte gegenüber dem Stand der Technik erreicht und wenn ja, welche? Lassen sich daraus Folgeprojekte ableiten?
Zwar ist die Erforschung der Molekularen Mechanismen der De-Halogenierung organischer Verbindungen in mikrobiellen Abbauwegen zunächst reine Grundlagenforschung. Dennoch hat diese Forschung eine hohe Relevanz für die Praxis: Die Dekontamination von Böden, die mit halogenierten organischen Verbindungen verunreinigt sind (z.B. bei der PVC Herstellung) ist ein drängendes Problem. Die Kenntnis der Mikroben, die eine entsprechende Abbauleistung erbringen können ist daher von unschätzbarem Wert für die Entwicklung von Bodensanierungskonzepten. Dies war auch ursprünglich die Motivation für diese Forschung, wie im Gutachten eingangs bereits erwähnt. In diesem Zusammenhang sei erwähnt, dass Frau Dr. Lechner in einem Projekt arbeitet, das sich mit der Dekontamination von mit Agent Orange kontaminierten Böden in Vietnam befasst (siehe Beitrag https://www.deutschlandfunk.de/der-lange-schatten-von-agent-orange-mit-bakteriengegen. 676.de.html?dram:article_id=375008)

h) Haben Sie sonstige Hinweise an die DFG
Zusammenfassend zeigt das vorliegende, nun abgeschlossene Projekt FOR1530 die Stärken der Forschungsförderung mit dem Instrument der Forschungsgruppe. Es konnte durch die Kombination komplementärer Expertisen von einzelnen, individuell starken, aber nicht international überragenden Arbeitsgruppen ein weltweit führender Forschungsverbund etabliert werden, der eine sehr komplexe Thematik so weit voranbringen konnte, wie es durch unkoordinierte Arbeiten einzelner Gruppen unmöglich gewesen wäre. Hervorheben möchte ich die Sprecherin Prof. Gabriele Diekert, die eine großartige Leistung vollbracht hat. Sie hat die richtigen Gruppen so zusammengeführt, so dass der Verbund mit 7 PIs groß genug war um die nötigen Expertisen zu vereinen, dennoch so übersichtlich, so dass die Kommunikation immer funktioniert hat. Die Früchte hat die Forschungsgruppe in der zweiten Förderperiode eingefahren, was den zeitlichen Horizont für die Beantwortung schwieriger Forschungsfragen aufzeigt. In dieser Hinsicht ist es sehr zu begrüßen, dass die DFG zuletzt den Förderzeitraum der einzelnen Periode auf vier Jahre verlängert hat."

Gutachten 2:
„Die FOR1530/2 (Diekert) hat sich einer spannenden, grundlegenden Frage zur Genomik, Biochemie und Physiologie von Mikroorganismen gewidmet, die in ihrem Energiestoffwechsel unter anaeroben Bedingungen halogenierte aliphatische und aromatische Kohlenwasserstoffe dehalogenieren. Dabei wurde mit Einsatz von komplementären Expertisen aus der Mikrobiologie, Biochemie/Enzymchemie und die Genetik die Mechanismen der Atmungskette, der reduktiven Dehalogenierung und der Regulation der Organohalid-respirierenden Bakterien aufgeklärt. Die gewählten Programmziele wurden erreicht und die molekularen Komponenten und Wirkmechanismen der Dehalogenierungsprozesse aufgeklärt. In Übereinstimmung mit dem vorliegenden abschließenden, fachnahen Gutachten, lässt sich festhalten, dass die FOR1530/2 (Diekert) in beiden Forschungsperioden sehr gut bis exzellent zusammengearbeitet hat und ein international sehr sichtbarer Verbund zu dieser komplexen Thematik aufgebaut wurde, wie es durch einzelne Forschungsaktivitäten der Gruppenmitglieder nicht möglich gewesen wäre. Dabei sind gerade in der 2. Förderperiode exzellente, gemeinsame Publikationsergebnisse aus mehreren Projekten entstanden (z.B. Kruse et al. Nat. Commun. 2018; Kunze et al. 2017, Nat. Commun.; Bommer et al. 2014 Science, Kublik et al. 2016, Environm. Microbiol.). Der Erfolg basierte auf einer erfolgreichen Weiterentwicklung und dem Ausbau des Themas durch die Leiterin G. Diekert. Die Nachwuchsförderung und Maßnahmen zur Gleichstellung waren vorbildlich. Es waren von Anfang an vier weibliche Projektleiterinnen (von insgesamt 7) im Konsortium von Ihnen waren drei Nachwuchswissenschaftlerinnen, auch die Mehrheit der PhDs war weiblich."

Ich freue mich, Ihnen dieses positive Votum mitteilen zu können. Die Berichtspflicht zu Ihrem Projekt ist damit erfüllt.

Für Ihre weiteren Forschungsarbeiten wünschen wir Ihnen viel Erfolg.

Mit freundlichen Grüßen

gez. Dr. Regina Nickel
Dieses Schreiben wurde elektronisch erstellt und versendet und trägt daher keine Unterschrift.

DFG

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