# Vereinigung für Allgemeine und Angewandte Mikrobiologie e.V.

## Section “Biology of Bacterial Natural Product Producers”


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Vereinigung für Allgemeine und Angewandte Mikrobiologie

Dear Attendees of the Conference,

We extend our warm welcome to the annual VAAM Symposium of the Section "Biology of Bacterial Natural Product Producers". It is our pleasure to host this esteemed scientific symposium at Saarland University in 2023 for the very first time.

The Scientific Organizing Committee has worked diligently to curate an engaging and diverse program. In this brochure, you will find the titles and authors of all the presentations, along with their corresponding abstracts. The scientific agenda includes keynote presentations by internationally renowned scientists, twenty-five talks by young researchers and more than 70 poster contributions. Session topics include topics ranging from microbial physiology and ecology to microbial genomics and metabolomics with the aim discovering novel bioactive natural products. Best poster presentations and talks will be awarded on the final day of the symposium!

We express our heartfelt gratitude to all those who have contributed in various ways to make this conference possible and hope that you enjoy both the scientific and social program!

Warm regards,

## The organizing team

Prof. Dr. Christine Beemelmanns,
Dr. Julian Hegemann,
Jun.-Prof. Dr. Alexey Gurevich,
Dr. Kenan Bozhüyük

Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS) together with Saarland University

HIPS HELMHOLTZ Institute for Pharmaceutical Research Saarland

UNIVERSITÄT DES SAARLANDES

trijathlon

# Symposium Program

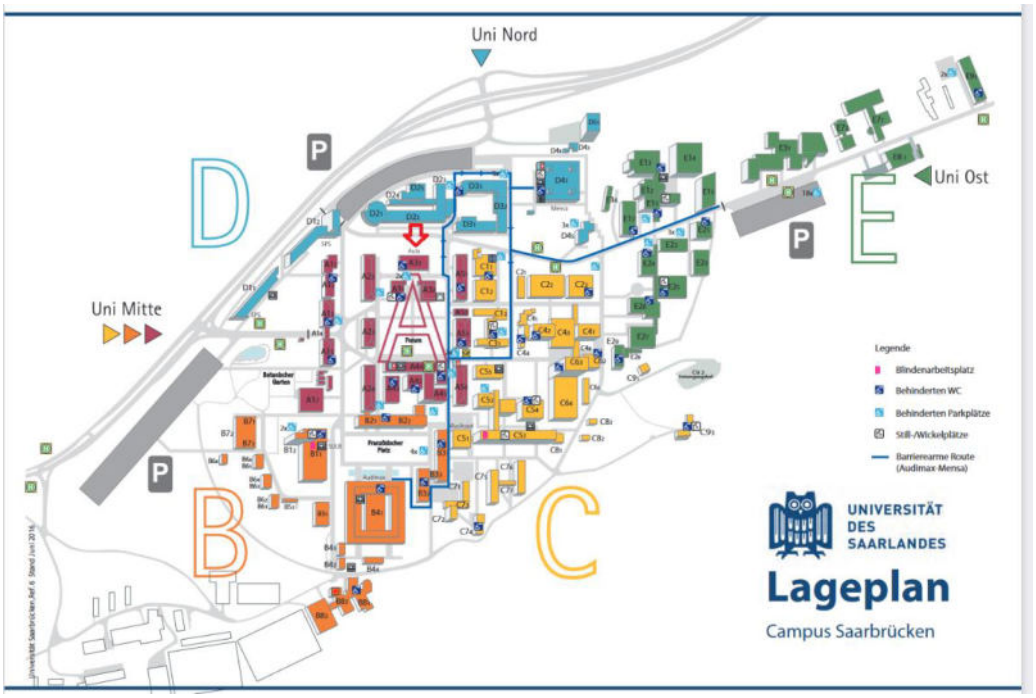
| WEDNESDAY | TOPIC | SESSION CHAIR |
|---|---|---|
| **12.00 – 14.00** | Arrival & Registration | |
| **14.00 – 14.15** | Introduction | **Christine Beemelmanns** |
| **14.15 – 15.00** | **Marnix Medema**<br>***Deciphering the chemical language of microbiomes*** | **Alexey Gurevich** |
| **15.00 – 16.20** | **Short talk session 1**<br>Thomas Booth<br>Tatiana Malygina<br>Ludek Sehnal<br>Azat Tagirdzhanov | **Alexey Gurevich** |
| **16.20 – 17.20** | Coffee break and poster session 1 (odd numbers) | |
| **17.20 – 17.50** | **Joleen Masschelein**<br>***Unveiling the iterative assembly of hybrid specialized lipid antibiotics*** | **Julian Hegemann** |
| **17.50 – 19.15** | **Short talk session 2**<br>Denis Iliasov<br>Jingyi Hu<br>Dardan Beqaj<br>Ben Scott | **Julian Hegemann** |
| **19.15 – 20.00** | Reception and poster session 2 (odd numbers) | |
| **20.00 – 22.00** | BBQ | |

| THURSDAY | TOPIC | SESSION CHAIR |
|---|---|---|
| **9.00 – 10.00** | **Short talk session 3**<br>Friederike Biermann<br>Li Su<br>Johannes Eckert | **Christine Beemelmanns** |
| **10.00 – 10.45** | **Pierre Stallforth**<br>***Natural Products From Interacting Microorganisms And Ancient Microbiomes*** | **Christine Beemelmanns** |
| **10.45 – 11.30** | Coffee break and poster session 3 (even numbers) | |
| **11.30 – 13.00** | **Short talk Session 4**<br>Jethro Hemmann<br>Leonard Präve<br>Franziska Höhn<br>Dmytro Bratiichuk | **Elke Dittmann** |
| **13.00 – 14.30** | Lunch | |
| **14.30 – 15.00** | **Section business** | **Christine Beemelmanns** |
| **15.00 – 15.45** | **Barrie Wilkinson**<br>***Obafluorin, a natural product inhibitor of threonyl-tRNA synthetase: biosynthesis and mechanisms of action and immunity*** | **Kenan Bezhüyük** |
| **15.45 – 16.30** | **Short talk Session 5**<br>Matiss Maleckis<br>Heng Li | **Kenan Bezhüyük** |
| **16.30 – 17.30** | Coffee break and poster session 4 (even numbers) | |

| THURSDAY | TOPIC | SESSION CHAIR |
|---|---|---|
| **17.30 – 18.00** | **Daniel Petras**<br>***From Molecules to Ecosystems – A Functional Metabolomics Toolbox to Study the Role and Fate of Small Molecules within Microbial Communities*** | **Julian Hegemann** |
| **18.00 – 19.00** | **Short talk Session 6**<br>Maksym Myronovskyi<br>Sofia Camila Bravo<br>Sebastian Greif | **Julian Hegemann** |
| **19.00 – 19.30** | Wolff Prize short talk | **Helge Bode** |
| **19.30 – 20.00** | Reception and all Poster | |
| **20.00 – 22.00** | Dinner in Aula | |

| FRIDAY | TOPIC | SESSION CHAIR |
|---|---|---|
| **9.00 – 9.30** | **Lena Barra**<br>***NAD-derived specialized metabolism*** | **Christine Beemelmanns** |
| **9.30 – 10.50** | **Short talk Session 7**<br>Matin Nuhamunada<br>Shrikrishnan Sankaran<br>Florian Hubrich<br>Chengzhang Fu | **Christine Beemelmanns** |
| **10.50 – 11.15** | Coffee break | |
| **11.15 – 11.30** | Prizes for poster and talks | **Conference Team** |
| **11.30 – 12.15** | **Helge Bode**<br>***Natural products from microbes and men*** | **Christine Beemelmanns** |
| **12.30 – 13.00** | Final words & Departure | |

Location: Saarland University, Aula, Campus UdS, Building A.3.3




**Train services to Saarbrücken:** High-speed ICE/TGV services are available from Frankfurt/Mannheim and Paris to Saarbrücken central station. Regional services run from Mainz, Trier and Strasbourg. At specific times it is worth leaving the regional train at Dudweiler station or Scheidt station and change for the bus.

**Bus services to Saarbrücken campus:** To get from Saarbrücken central station to the university campus, take either bus number 102 (to 'Dudweiler-Dudoplatz') or bus numbers 112 or 124 (to 'Universität'). These services run every 30 minutes. Buses also run to the university from the districts of Saarbrücken, St. Ingbert and Neunkirchen. A shuttle bus organized by AStA runs between the Saarbrücken and Homburg university campuses (**Bus stops on campus:** Universität Botanischer Garten, Universität Campus, Universität Mensa, Universität Busterminal)

# Abstracts of Invited Speakers
# (chronological order)

**Marnix Medema** is a Professor of Bioinformatics at Wageningen University. His research group develops and applies algorithms for the (meta)genomic identification and functional prediction of microbial biosynthetic pathways, with the aim to unravel the chemical language of microbiomes. He built and co-coordinates the development of the antiSMASH software for identification of biosynthetic gene clusters and developed various additional algorithms to chart their diversity and identify their functional roles in microbiomes. Medema is recipient of NWO Rubicon, Veni and Vidi fellowships and an ERC Starting Grant, and has coordinated several international consortia studying bacterial specialized metabolites. He received several prizes for his work, including the NBIC Young Investigator Award. He is editorial board member of Natural Product Reports, mSystems and FEMS Microbes, and senior editor of ISME Communications. Also, he is member of the scientific advisory board of Hexagon Bio and co-founder of Design Pharmaceuticals. Since 2020, he also served as Van der Klaauw visiting professor of theoretical biology at Leiden University.

### Deciphering the chemical language of microbiomes

**Abstract:** Microbial specialized metabolites are important mediators of molecular interactions between microbes as well as with the host, and in a way constitute the 'chemical language' of the microbiome. Hence, they are of great importance from both ecological and clinical perspectives. A range of computational methods have been developed to identify these molecules and the metabolic gene clusters that encode their production, and to assess their biological activities. Here, I will highlight recent work performed in my research group on developing and applying these approaches to accelerate natural product discovery, as well as to study the roles of these pathways in microbe-microbe and host-microbe interactions in microbiomes. Specifically, I will provide examples of how we are applying these methods to identify BGCs responsible for disease-suppressive phenotypes of rhizosphere microbiomes.

**Joleen Masschelein** has an M.Sc. in Bioscience Engineering (2009) and obtained her PhD in 2015 at the Department of Biosystems at KU Leuven (Belgium). She was subsequently awarded a Marie-Sklodowska Curie Individual Fellowship from the European Commission to join the group of Prof. Greg Challis in the Department of Chemistry at the University of Warwick (UK). In 2017, she moved to the Laboratory for Medicinal Chemistry at KU Leuven as a postdoctoral research fellow of the Research Foundation – Flanders. In 2020, she was appointed as an Assistant Professor at the Department of Biology at KU Leuven and as a Group Leader at the VIB-KU Leuven Center for Microbiology. She is also a Visiting Professor at the Tianjin Institute for Industrial Biotechnology in China. In 2023, she was awarded an ERC Starting Grant and she currently serves on the editorial advisory boards for the journals *JACS Au* and Synthetic and Systems Biotechnology. Her research is focused on the discovery, biosynthesis and mode of action of bioactive natural products from host-associated bacteria. She is particularly interested in microbiome biosynthetic engineering for *in vivo* therapeutic or agrochemical applications.

## Unveiling the iterative assembly of hybrid specialized lipid antibiotics

**Abstract:** Microorganisms produce a wealth of specialized metabolites with highly diverse chemical structures and important industrial applications. The zeamines are an unusual group of long-chain polyamine antibiotics produced by host-associated bacteria that exhibit potent activity against a broad spectrum of organisms, including bacteria, fungi, plants and nematodes. They are assembled by an unprecedented combination of polyketide, nonribosomal peptide and polyunsaturated fatty acid (PUFA) synth(et)ase-like biosynthetic machinery. A bioinformatic search has indicated that such hybrid biosynthetic pathways are not an isolated occurrence and are likely involved in the biosynthesis of a range of bioactive, hybrid specialized lipid metabolites that have remained elusive so far. In this study, we deciphered the iterative biosynthetic logic of zeamine assembly. The zeamine II pathway has evolved from PUFA synthases and has acquired additional functionalities, including a *cis*-acting aminotransferase, ketoreductase and thioester reductase domain. Using a combination of bioinformatic analyses, *in vivo* mutagenesis, *in vitro* enzymatic assays, chemical synthesis and X-ray crystallography, we functionally characterized each catalytic domain and elucidated their substrate selectivity. Moreover, we reconstituted the entire zeamine II pathway *in vitro*, providing important insights into the iterative programming of this unusual assembly line. Finally, we also provide insights into an enzyme that confers zeamine resistance by targeting the polyamine chain. Our findings thus provide insights in a new class of hybrid specialized lipid metabolites and open up new opportunities for rational engineering of novel polyamine analogues with improved pharmacological properties.

**References**

[1] *Chem. Sci.* 2015, **6**, 923–929; [2] *Appl. Environ. Microbiol. 2015,* **81**, 1139–1146; [3*] PLoS One,* 2013, **8**, e54143

**Pierre Stallforth** studied Chemistry at the University of Oxford, UK. He obtained his PhD under the guidance of Prof. Peter H. Seeberger at ETH Zurich. He then moved to Harvard Medical School where he did his postdoc in the laboratory of Prof. J. Clardy. In December 2013, he moved to the Leibniz-HKI, Jena, Germany as an independent Junior Research Group Leader. In January 2020 he was promoted to head of the Department of Paleobiotechnology. Since December 2021 he is a Professor of Bioorganic Chemistry and Paleobiotechnology at the Friedrich Schiller University Jena. His research focus lies on understanding the role in polymicrobial interactions in modern and ancient microbiomes.

## NATURAL PRODUCTS FROM INTERACTING MICROORGANISMS AND ANCIENT MICROBIOMES

**Abstract:** Microbial natural products have been an indispensable source of novel therapeutic agents. The search for new bioactive natural products has prompted scientists to exploit environmental niches in which the production of these compounds can be anticipated. Microbial predator–prey interactions are particularly rich sources of natural products. We describe one such interaction in which bacterivorous amoebae and their prokaryotic prey meet. Amoebae are voracious and ubiquitous predators to bacteria that cause constant depletion of huge bacterial reservoirs. This puts both organisms under strong evolutionary selection pressure: the bacteria have evolved mechanisms to prevent grazing and the amoebae must counteract or surmount these mechanisms in order to survive.[1,2] We are particularly interested in the biosynthesis and evolution of these amoebicidal microbial natural products and we shine light on polymicrobial natural product modifications within this context.[3-5] Recently, we have exploited means to gain access to microbial natural products diversity the past. To this end, we use ancient bacterial DNA to identify and eventually express biosynthetic genes.[6]

**References:**

[1] M. Klapper, S. Götze, R. Barnett, K. Willing, P. Stallforth, *Angew. Chem. Int. Ed.* **2016**, *55*, 8944–8947.

[2] J. Arp, S. Götze, R. Mukherji, D. J. Mattern, M. García-Altares, M. Klapper, D. A. Brock, A. A. Brakhage, J. E. Strassmann, D. C. Queller, B Bardl, K Willing, G. Peschel, P. Stallforth, *Proc. Natl. Acad. Sci. USA.* **2018**, *115*, 3758–3763.

[3] S. Zhang⁺, R. Mukherji⁺, S. Chowdhury, L. Reimer, P. Stallforth, *Proc. Natl. Acad. Sci. U. S. A.* **2021**, *118*, e2013759118.

[4] S. Götze, R. Vij, K. Burow, N. Thome, L. Urbat, N. Schlosser, S. Pflanze, R. Müller, V. G. Hänsch, K. Schlabach, L. Fazlikhani, G. Walther, H.-M. Dahse, L. Regestein, S. Brunke, B. Hube, C. Hertweck, P. Franken, P. Stallforth***** *J. Am. Chem. Soc.* **2023**, *145*, 2342.

[5] S. Zhang, K. Schlabach, V. H. Pérez Carrillo, A. Ibrahim, A. Komor, R. Mukherji, S. Chowdhury, L. Reimer, C. Hertweck, U. A. Hellmich, P. Stallforth *submitted*

[6] M. Klapper⁺, A. Hübner⁺, A. Ibrahim⁺, I. Wasmuth, Maxime Borry, V. G. Haensch, S. Zhang, W. K. Al-Jammal, H. Suma, J. A. Fellows Yates, J. Frangenberg, I. M. Velsko, S. Chowdhury, R. Herbst, E. V. Bratovanov, H.-M. Dahse, T. Horch, C. Hertweck, M. R. González Morales, L. G. Straus, I. Vilotijevic, C. Warinner, P Stallforth *Science* **2023**, *380*, 619.

**Barrie Wilkinson** is a chemical biologist working on various aspects of bacterial enzymology, natural products chemistry and molecular genetics. He is a Group Leader in Molecular Microbiology at the John Innes Centre (JIC). He was trained at the Universities of Leeds (BSc in chemistry & PhD with Richard B. Herbert), Washington (postdoc with Heinz G. Floss) and Cambridge (postdocs with Jim Staunton and Peter F. Leadlay). In 2013 Barrie co-founded Isomerase Therapeutics Ltd (Cambridge, UK) to develop natural products as potential therapeutics targeted at peptidyl-prolyl *cis-trans* isomerases. Since 2019 he has been the lead of JICs Institute Strategic Programmes *Molecules from Nature* and *Harnessing Biosynthesis for Sustainable Food & Health*. Prior to joining JIC Barrie spent 16 years in the pharmaceutical and biotechnology industry, first at GlaxoWellcome and then at Biotica Technology Ltd, a UK biotechnology company exploiting polyketide natural products derived from *Streptomyces*.

## Obafluorin, a natural product inhibitor of threonyl-tRNA synthetase: biosynthesis and mechanisms of action and immunity

**Abstract:** Obafluorin is a *Pseudomonas fluorescens* antibacterial natural product that inhibits threonyl-tRNA synthetase (ThrRS).[1] It acts as a broad-spectrum antibiotic against a range of clinically relevant pathogens and comprises a strained β-lactone ring decorated with catechol and 4-nitro-benzyl moieties. The catechol moiety is widespread in nature and its role in the coordination of ferric iron has been well-characterised in siderophores and Trojan horse antibiotics. Here we use a combination of mutasynthesis, chemical biology and structural biology to delineate the obafluorin mechanism of action and understand how a *P. fluorescens* immunity determinant avoids inhibition. We use *P. fluorescens* biosynthetic mutants to generate obafluorin analogues with modified catechol moieties and demonstrate that an intact catechol is required for both antibacterial activity and inhibition of the ThrRS molecular target. In agreement with recent work,[2] we show that the obafluorin catechol coordinates $Zn^{2+}$ in the ThrRS active site, orientating the beta-lactone moiety for nucleophilic attach by an invariant tyrosine residue and formation of a covalent intermediate that mimics the threonyl-tRNA enzymatic product. Structural data for the immunity enzyme ObaO provides a rationale for its resistance to obafluorin inhibition. Despite the strong association with zinc in the enzyme active site, obafluorin is a weak $Zn^{2+}$ binder *in vitro*, contrasting with a strong, specific 1:1 interaction with $Fe^{3+}$. We use bioassays with siderophore transporter mutants to probe the role of the obafluorin catechol in $Fe^{3+}$-mediated uptake. Surprisingly, obafluorin does not behave as a Trojan horse antibiotic but instead exhibits increased antibacterial activity in the presence of $Fe^{3+}$. We further demonstrate that $Fe^{3+}$ binding prevents the hydrolytic breakdown of the β-lactone ring, and likely improved passive uptake, revealing a hitherto unreported function for the catechol moiety in natural product bioactivity.

**References:** [1] Scott et al. (2019) *ACS Chem. Biol*. **14**:2663-2671; [2] Qiao et al. (2023) *Commun. Biol.* **6**:107.

**Daniel Petras** is biochemist with a background in bioanalytical and natural product chemistry. He received his master's degree in biotechnology from the University of Applied Science Darmstadt and his PhD in biochemistry from the Technical University Berlin in 2016. His thesis in the group of Roderich Suessmuth focused on the discovery, structure elucidation and biosynthesis of different peptide toxins, including albicidins, a group of potent antibiotics. For his postdoctoral research, Daniel joined the lab of Pieter Dorrestein at the University of California San Diego, where he focused on the development of large-scale environmental metabolomics methods. In 2021, Daniel launched the Functional Metabolomics Lab at the University of Tübingen as an independent Junior Research Group. The work of his group focuses on the development and application of mass spectrometry-based methods to visualize and functionally assess chemical exchange within microbial communities.

## From Molecules to Ecosystems – A Functional Metabolomics Toolbox to Study the Role and Fate of Small Molecules within Microbial Communities

**Abstract:** The chemical composition of the ocean's community metabolome represents a fascinating source of chemical entities that are fundamentally important for ecosystem function and planetary processes such as global carbon cycling. Thanks to recent advances in tandem mass spectrometry and computational data analysis tools, we can identify a wide range of metabolites out of this ultra-complex mixture and propose some of their activities through literature knowledge. However, the number of known metabolites and activities represents only a small fraction of all compounds we can detect in these environments. To fully map out the structural and bioactivity space, new methods are needed, as traditional isolation and bioactivity studies do not scale to contemporary non-targeted metabolomics workflows. To address this need, we develop functional metabolomics tools that integrate liquid chromatography tandem mass spectrometry with metagenomics as well as native mass spectrometry and proteomics. In combination with molecular networking, these workflows allow us to connect the marine meta-metabolome to community composition and protein-metabolite interactions. Taken together, our results provide new insights in the enormous chemical complexity of marine microbial communities and highlight the potential of functional metabolomics workflows for the linking of environmental metabolomics data with microbial communities and biological mechanisms.

**Lena Barra** studied chemistry at the Technical University of Braunschweig and subsequently joined the group of Prof. Dr. Jeroen S. Dickschat at the University of Bonn to pursue her PhD, working on microbial terpene biosynthetic pathways and the design and application of isotopically labelled compounds for mechanistic investigations. For her postdoctoral studies, she joined the group of Prof. Dr. Ikuro Abe at the University of Tokyo where she worked on unravelling the biosynthesis of a group of structurally unusual azaindane natural products, which were demonstrated to originate from nicotinamide adenine dinucleotide (NAD). In May 2022, she has been appointed as Tenure-Track-Professor at the University of Konstanz and leads an independent research group, focusing on the discovery and investigation of non-canonical natural product pathways.

## NAD-derived specialized metabolism

**Abstract:** Nicotinamide adenine dinucleotide (NAD) is a pivotal metabolite for all living organisms and functions as a diffusible electron acceptor and carrier in central catabolic processes[1]. During biosynthetic investigations on the structurally unusual anti-cancer compound altemicidin[2] (**1**), we discovered a novel function for NAD as a building block in secondary metabolite biosynthetic pathways (**Fig.1a**)[3]. The gatekeeping enzyme of the pathway (SbzP) constitutes a novel family of pyridoxal phosphate (PLP)-dependent proteins, catalyzing formation of the 6-azatetrahydroindane core scaffold via a sophisticated (3+2)-cycloaddition reaction, utilizing S-adenosyl methionine (SAM) as cosubstrate. Functional homologs of SbzP are widely distributed in the bacterial kingdom and bioinformatic analyses indicate that NAD-derived secondary metabolism represents a promising and yet untapped resource for the discovery of novel natural products and unqiue enzyme chemistries.

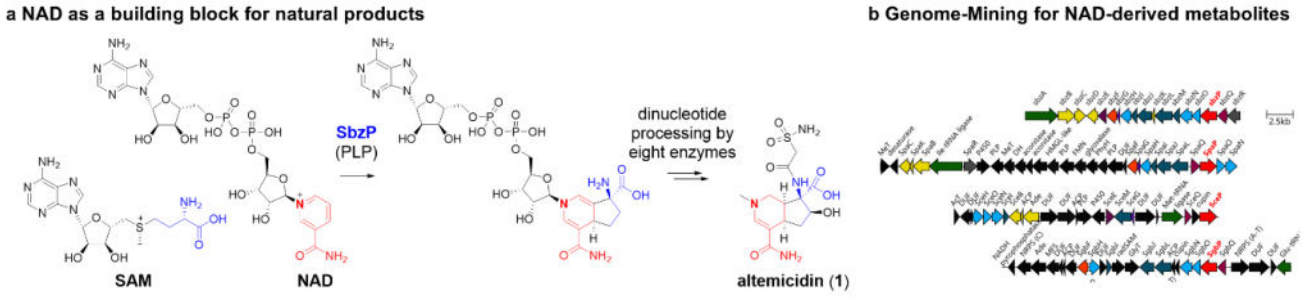



***Fig.1 a.*** *Discovered PLP-mediated 6-azatetrahydroindane scaffold formation by SbzP utilizing NAD and SAM as substrates.* ***b.*** *Representative biosynthetic gene clusters discovered by genome mining.*

**References:**

[1] Walsh, C. T. & Tang, Y. *The Chemical Biology of Human Vitamins*, RSC, (2019).

[2] Hu, Z., Awakawa, T., Ma, Z. & Abe, I. *Nat. Commun.* **10**, 1-10 (2019).

[3] Barra, L., Awakawa, T., Shirai, K., Hu, Z., Bashiri, G. & Abe, I. *Nature* **600**, 754-758 (2021).

## Helge B. Bode

Max Planck Institute for Terrestrial Microbiology (MPI)
Department of Natural Products in Organismic Interactions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|---|---|
| 1997 | Diploma in Chemistry, University of Göttingen (D) |
| 2000 | Dr. rer. nat., Organic Chemistry, University of Göttingen (D) |
| 2001 | Diploma in Biology, University of Göttingen (D) |
| 2000-2001 | Postdoc, Biomolecular Chemistry, University of Göttingen (D) |
| 2001-2002 | Postdoc, German Research Center for Biotechnology (D) |
| 2002-2003 | Postdoc, Department of Biochemistry, Stanford University (USA) |
| 2004-2005 | Juniorprofessor, Natural Product Biotechnology, Pharmaceutical Biotechnology, Saarland University (D) |
| 2006-2010 | Emmy Noether Fellow (DFG), Saarland University (D) and Goethe University Frankfurt |
| 2008-2017 | Merck-endowed chair (W3) for Molecular Biotechnology, Goethe University Frankfurt (D) |
| 2018-2022 | Professor for Molecular Biotechnology, Goethe University Frankfurt (D) |
| Since 2020 | Director and Head of the Department of Natural Products in Organismic Interactions at the MPI Marburg |
| Since 2022 | Professor for Chemical Biology, Department of Chemistry, Philipps-Universität Marburg |
| Since 2022 | Goethe Research Professor for Molecular Biotechnology, Goethe University Frankfurt (D) |

## Natural products from microbes and men


**Abstract:** Microbial natural products are a major source and inspiration for bioactive drugs in agriculture, animal health and medicine. However, we know only a small fraction of these microbial natural products and we are missing tools to broaden their chemical diversity beyond what we can currently find in nature. In my talk, I will present methods from our lab to (i) activate and/or manipulate biosynthetic gene clusters from proteobacteria for the efficient production of desired natural products and to (ii) use the engineering of non-ribosomal peptide synthetases (NRPS) for the generation of new peptides and to understand biosynthesis pathways in molecular detail.