GRK2158 Symposium

“Natural compounds and analogs against therapy resistant tumours and microorganisms”

September 17th–21st 2018

Beijing, China

Conference Center of Medical Health Center, Peking University

HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

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Research Training Group GRK2158

“Natural products and natural product analogs against therapy-resistant tumors and microorganisms: new lead structures and modes of action”

The core subjects of pharmaceutical research are the unravelling of molecular resistance mechanisms against pharmacologically active compounds as well as the search for new bioactive compounds that can overcome either intrinsic or extrinsic resistance.

These important topics will be investigated within the Research Training Group GRK2158 as exemplified by chemoresistant tumors and infections with chemoresistant microbial pathogens. Both forms of diseases are characterized by numerous resistance mechanisms against currently available drugs which may either weaken the success of drug therapy or which will render it completely ineffective. Known resistance mechanisms of tumors and microbial pathogens show functional similarities. Efforts aiming at a combined study of antitumor and of antimicrobial activities will thus lead to a scientific added value, especially as microorganisms often serve as model systems for research on more complex eukaryotic cells.

Natural products and analogs inspired by natural products that are derived from stress exposed and hitherto rarely investigated marine organisms and fungal endophytes (e.g. from the People’s Republic of China) will serve as a pool for new lead structures and inspirations for novel molecular tools that will help in unravelling molecular modes of action and resistance mechanisms. The Research Training Group is highly interdisciplinary. It enables graduate students to acquire comprehensive knowledge in important basic as well as applied aspects of modern preclinical drug discovery and will qualify them for future sophisticated professional activities.

The long-standing cooperation between the Institute of Pharmaceutical Biology of the University of Duesseldorf and Peking University is not only a basis for a fruitful exchange of knowledge about natural products, but has now led to the joint organization of this year's symposium in Beijing, China.

The Research Training Group GRK2158 is funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation).

Organizing committee

German coordinators:

Prof. Dr. Peter Proksch (Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Germany)
Tel: (49)-211-8114163
Email: proksch@uni-duesseldorf.de

Dr. Martina Holz (Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Germany)
Tel: (+49)-211-8115592
Email: grad2158@uni-duesseldorf.de

Chinese coordinators:

Prof. Dr. Wenhan Lin (School of Pharmaceutical Sciences, Peking University)
Tel: (86)-010-82806188
Email: whlin@bjmu.edu.cn

Dr. Dong Liu (School of Pharmaceutical Sciences, Peking University)
Email：liudong_1982@126.com
(response for restaurant reservation, air-port pick-up, transportation, city-touring, hotel check-in and check-out, meeting room reservation, coffee break)

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

北京大學
PEKING UNIVERSITY

Important Addresses and Telephone numbers

Conference Center of Medical Health Center, Peking University

No.38 Xueyuan Road, Haidian District, Beijing, China
Name：北京大学医学部会议中心
Address：北京市 海淀区 学院路 38 号

Master Inn

No.38 Xueyuan Road, Haidian District, Beijing, China
Name：赢家商务酒店
Address：北京市 海淀区 学院路 38 号

Vision Hotel

No.39 Xueyuan Road, Haidian District, Beijing, China
Name：北京唯实酒店
Address：北京市 海淀区 学院路 39 号

Travel and City Maps

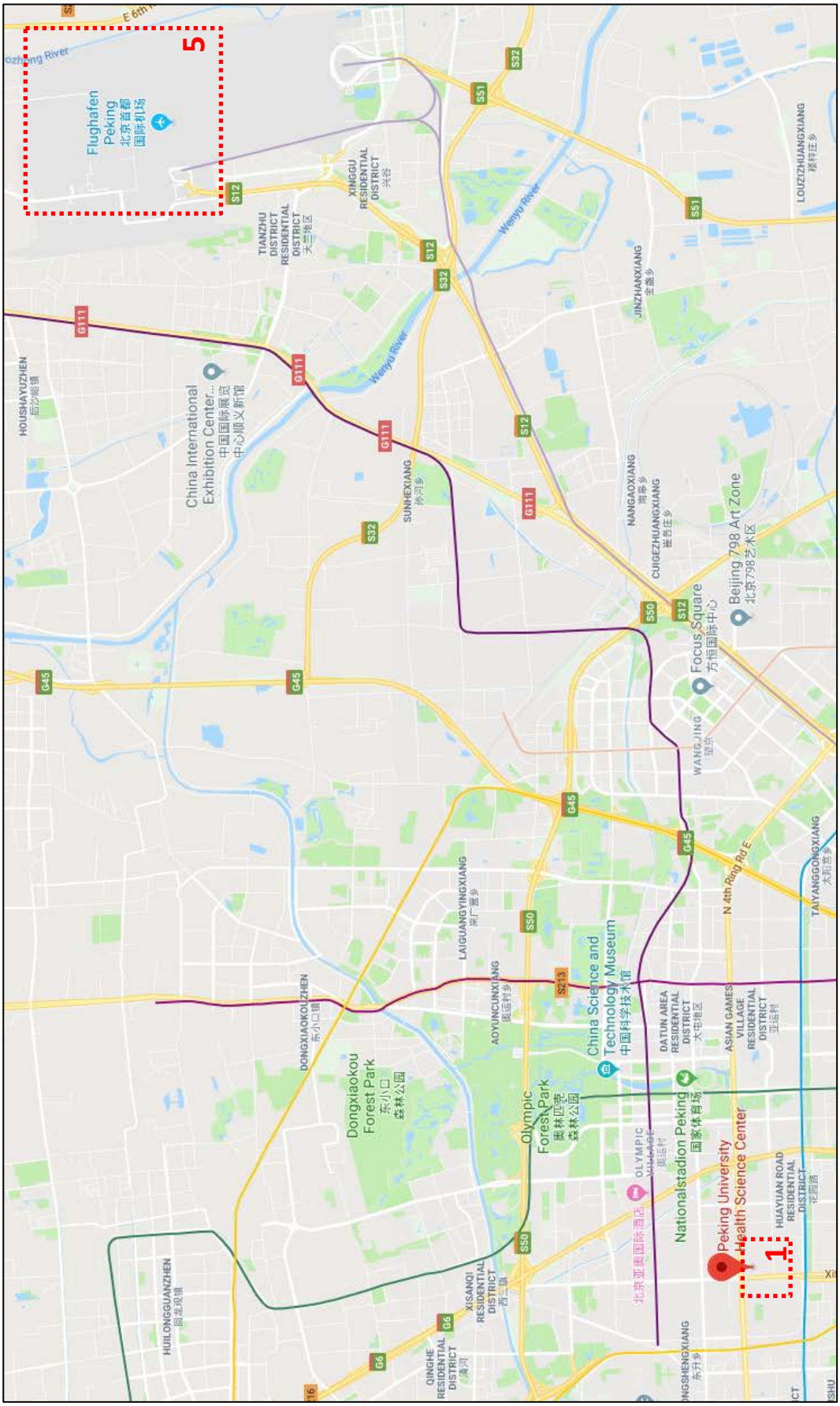
1	Peking University Health Science Center, Haidian District, Beijing, China
2	Master Inn, No.38 Xueyuan Road, Haidian District, Beijing, China
3	Vision Hotel Beijing, No.39 Xueyuan Road, Haidian District, Beijing, China
4	Xi Tu Cheng Subway Station

Campus

1 Peking University Health Science Center, Haidian District, Beijing, China

2 Master Inn, No.38 Xueyuan Road, Haidian District, Beijing, China

Airport Beijing



1 Peking University Health Science Center, Haidian District, Beijing, China

5 Beijing Capital Airport

Travel advice

All participants arriving on September 17th 2018 (Flight: LH 722, 10:35 am, Beijing Capital Airport) will be picked up and brought to the hotel by bus. All participants departing on September 22nd 2018 (Flight: LH 723, 12:35 pm, Beijing Capital Airport) will be brought to the airport by bus.

Those who arrive and leave individually can use the transportation as described here:

1 **From Beijing Capital Airport to Vision Hotel** (No. 39 Xueyuan Road, Haidian District, Beijing China)

Subway:

Take the ***Airport Express*** (Every 10 mins) to Subway Station ***San Yuan Qiao***

Change to ***Subway Line 10*** (Direction of Che Dao Gou) to Subway Station ***Xi Tu Cheng*** (Approximately 18 mins, 8 stations)

Then walk approx. 650 m to Vision Hotel.

Taxi:

Distance between airport and hotel is around 30-35 km. It will cost around 90 RMB + 10 RMB (fee of airport highway)

2 **From Beijing Capital Airport to Master Inn** (No. 38 Xueyuan Road, Haidian District, Beijing China)

Subway:

Take the ***Airport Express*** (Every 10 mins) to Subway Station ***San Yuan Qiao***

Change to ***Subway Line 10*** (Direction of Che Dao Gou) to Subway Station ***Xi Tu Cheng*** (Approximately 18 mins, 8 stations)

Then walk approx. 1 km to Master Inn.

Taxi:

Distance between airport and hotel is around 30-35 km. It will cost around 90 RMB + 10 RMB (fee of airport highway).

3 **From Vision Hotel to Peking University Health Science Center**

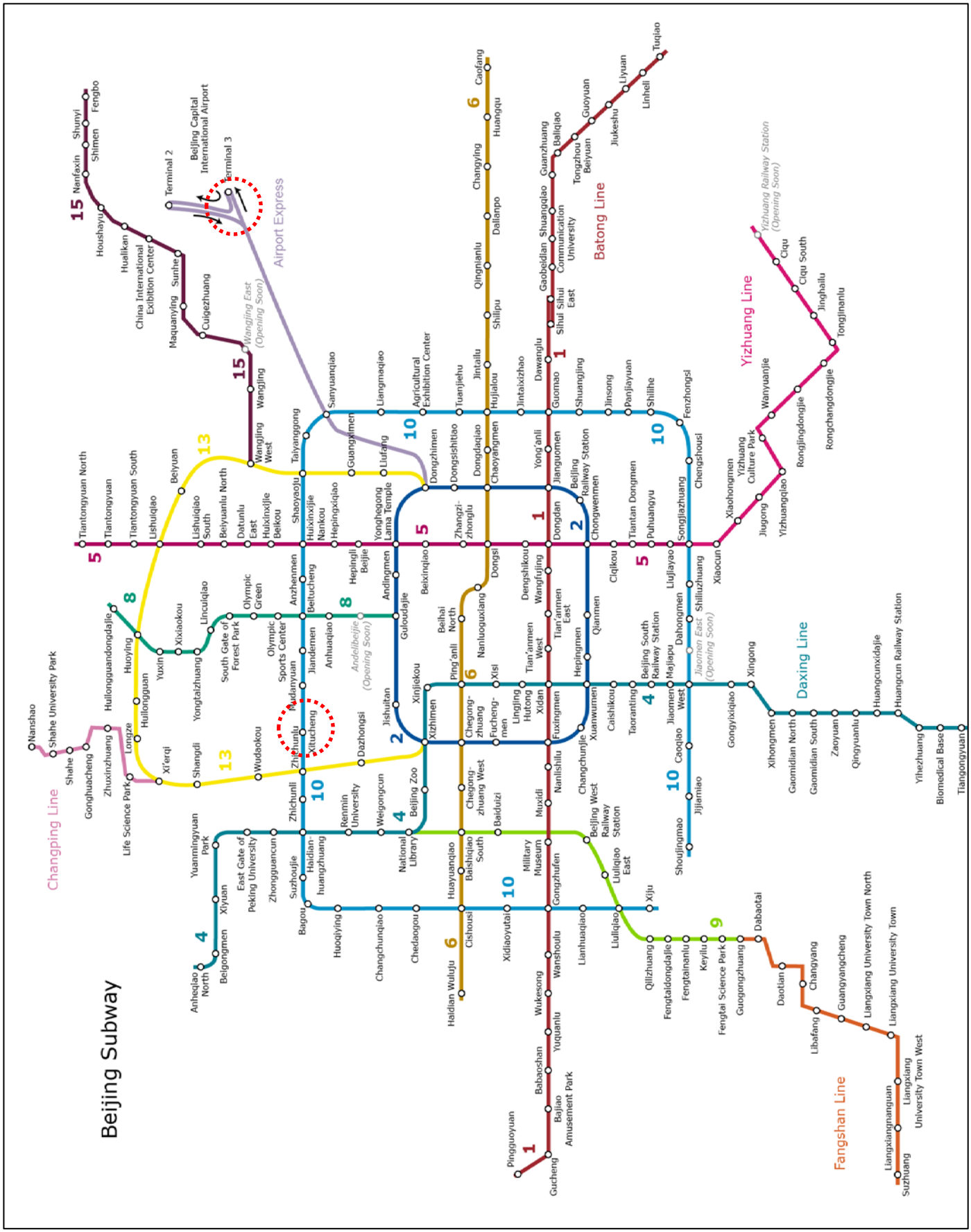
Turn right on Xitucheng Road

Cross Xitucheng Road as soon as possible and Change directions

Walk on Xitucheng Road and Xueyuan Road approx. 850 m

Then turn right to Peking University Health Science Center

Beijing Subway Map



Symposium program

September 17th 2018

10:35	Arrival at Beijing Capital Airport, China
12:00	Transportation from Airport to Hotels & Check-in
18:00	**Welcome Banquet at restaurant of MasterInn**

September 18th 2018

09:00	Arrival at Conference Center Registration and Check- in
09:20	**Welcome and Introduction** Peter Proksch & Wenhan Lin
9:40 – 11:30	**1st Session** **Chair: Peter Proksch**
09:40	**Targeting recalcitrant bacteria with natural-sourced molecules** Rainer Kalscheuer
10:10	**Antitubercular activity of synthetic Callyaerins** Yvonne Gröner
10:25	**Concise synthesis of natural products and kinase inhibitors by metal catalysis initiated One-Pot methodologies** Thomas J.J. Müller
10:55	**Identification of new natural products with anti-microbial activity against Apicomplexa and multiresistant gram-negative rods (4MRGN)** Shabnam Shaneh Sazzadeh
11:10	**Diketopiperazine alkaloids from marine-derived fungus *Aspergillus* sp.** Chao-Yi Wang
11:30 – 13:00	**Lunch Break**

13:00 – 15:15	**2nd Session** **Chair: Bin-Gui Wang**
13:00	**Antibacterial and antiviral natural products from marine organisms collected from the South China Sea** Chang-Yun Wang
13:30	**Chemical diversity and biological activity of secondary metabolites from *Artemisia argyi* and its endophytic fungi** Xiao-Shan Shi
13:45	**Predicting orphan allosteric binding sites** Holger Gohlke
14:15	**Virtual screening-based identification and molecular dynamics study of Nisin resistance protein (NSR) lead inhibitors** Nicola Porta
14:30	**Resistance against lantibiotic mediated by specific operon detected in human pathogens** Sander H. J. Smits
15:00	**Functional and structural studies of the Nisin resistance protein NSR of *Streptococcus agalactiae*** Julia Zaschke-Kriesche
15:15 – 16:30	***Poster Session & coffee break***
16:30 – 17:30	***Sino-German student Meeting***
17:30	**Dinner**

September 19th 2018

9:00 – 10:30	3rd Session Chair: Thomas J.J. Müller
09:00	**Chemoenzymatic natural product synthesis** Jörg Pietruszka
09:30	**Towards the total synthesis of heterobiaryl natural products and their derivatives** Julian Greb
9:45	**Using photo-affinity labeling approach for the target identification of two marine bioactive compounds** Jian-Rong Liu
10:15	**Diversity-oriented one-pot synthesis of novel active agents against therapy resistant tumors and infections** Daniel Drießen
10:30 – 10:45	**Coffee Break**
10:45 – 12:00	**4th Session** **Chair: Chang-Yun Wang**
10:45	**Establishing the autophagy-inducing protein complexes as targets for cancer therapy** Björn Stork
11:15	**Identification of autophagy-modulating natural products and derivatives for the elimination of therapy-resistant tumor cells** Jana Deitersen
11:30	**Chemical diversity of terpenoids from the deep sea-derived fungus *Aspergillus wentii* SD-310** Xin Li
11:45	**Expanding the metabolic profile of the endophytic fungus *Humicola grisea*** Nam Michael Tran-Cong

12:00 – 13:30	**Lunch Break**
13:30 -15:15	**5th Session** **Chair: Rainer Kalscheuer**
13:30	**Probiotics inspired antibiotics to target superbugs** Kui Zhu
14:00	**Diversified metabolites from marine derived fungi** Bin-Gui Wang
14:30	**From selectivity to targeted promiscuity** Holger Stark
15:00	**Natural compounds and small molecules targeting the histamine H_4 receptor** Annika Frank
15:15 – 15:30	**Coffee Break**
15:30 – 16:30	**6th Session** **Chair: Yijia Lou**
15:30	**Plasmacytoid dendritic cells and type I interferon as immunomodulators in infectious diseases** Stefanie Scheu
16:00	**Identifying immunological properties of natural products for the treatment of chemoresistant tumors and bacterial pathogens** Lisa Richter
16:15	**Identifying bioactive natural compounds from mangrove-derived endophytic fungi** Ling-Hong Meng
16:30 – 17:30	**Lab viewing**
17:30	**Dinner**

September 20th 2018

9:00 – 10:45	7th Session Chair: Holger Stark
09:00	**Targeting mechanisms of DNA damage response (DDR) to overcome anticancer drug resistance of tumor cells** Jana van Stuijvenberg
9:15	**The deletion of a histone deacetylase gene (*PMG11_08486*) leads to secondary metabolic changes of penicillic acid and brasiliamide in *Penicillium brasilianum*** Bo-Chuan Yuan
09:30	**Cancer-specific pro-apoptotic effects of the mycotoxin viriditoxin** Fabian Stuhldreier
09:45	**Dxr as target for anti-infective drug discovery: Synthesis, antiplasmodial properties and structural biology of reverse fosmidomycin derivatives** Thomas Kurz
10:15	**Synthesis and biological evaluation of novel panobinostat derivatives** Marc Pflieger
10:30 – 10:45	**Coffee Break**
10:45 – 12:00	**8th Session** **Chair: Wenhan Lin**
10:45	**Molecular mechanism of S-nitrosoglutathione on ultrastructure of pancreatic islet beta cells in db/db mice** Yijia Lou
11:15	**Application of high-content imaging for the study of apoptosis induction by novel anti-cancer agents** Chenyin Wang
11:30	**The genome mining and synthetic biology of diterpenoids from marine and plant endophytic bacteria** Dong-Hui Yang

11:45 – 12:00	**Closing Remarks**
	Wenhan Lin & Peter Proksch
12:00 – 13:00	**Lunch Break**
13:00 – 17:00	**Visit of Summer Palace**
18:00	**Dinner**

September 21st 2018

9:00	**Excursion to the Great Wall**
18:00	**Farewell Dinner**

September 22nd 2018

9:00	Transportation from hotels to airport, Flight number: LH 723
	(Departure at 12:35)

Abstracts of talks

Targeting recalcitrant bacteria with natural-sourced molecules

Rainer Kalscheuer, Nidja Rehberg, Lasse van Geelen
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Germany

Antibacterial chemotherapy is significantly complicated by the rapid global spreading of multi-drug resistant mutants. While the drug development pipeline is still relatively well-filled for Gram-positive bacteria such as Staphylococcus aureus, there is an urgent need to develop new treatment options particularly for recalcitrant bacterial pathogens such as Mycobacterium tuberculosis. In addition, certain bacterial subpopulations such as biofilms exist that are characterized by high intrinsic drug-tolerance and are largely unresponsive to conventional bacterial antibiotics. Our group is focusing on developing novel lead compounds for targeting these recalcitrant bacterial pathogens mainly using natural-sourced molecules as starting point. In addition to employing conventional methodologies in antibacterial drug discovery, special approaches need to be followed for detection and quantification of the desired bioactivites such as anti-biofilm activity or synergism with approved antibiotics. As successful examples, we will report on the discovery of the natural compounds chlorflavonin and 3-O-methylbutylgallic acid, which have been isolated from the endophytic fungus Mucor irregularis or from the Nigerian mistletoe Loranthus micranthus, respectively, and both show potent antibacterial potency against M. tuberculosis. While chlorflavonin targets branched-chain amino acid biosynthesis, 3-O-methylbutylgallic acid inhibits fatty acid desaturation. Both compounds are particularly characterized by potent synergism with certain anti-TB drugs.

Antitubercular activity of synthetic Callyaerins

Yvonne Gröner[1], Florian Schulz[2], Nidja Rehberg[1], Peter Proksch[1], Markus Kaiser[2] and Rainer Kalscheuer[1]
[1] Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Germany.
[2] Center of Medical Biotechnology, Chemical Biology, University of Duisburg-Essen

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*M. tb*), is still one of the world's most prevalent infectious diseases. In 2016, there were 10.4 million estimated new cases of TB and 1.3 million deaths. Drug resistance is a major problem in TB therapy with 490,000 cases in 2016 [1], some of which are resistant to all four core anti-TB drugs [2]. A promising source for new TB drugs are natural compounds, like members of the Callyaerin family, a unique class of sponge-derived peptides isolated from the Indonesian sponge *Callyspongia aerizusa* [3]. The research group of Professor Kaiser (University of Duisburg-Essen) established a robust chemical synthesis scheme, overcoming the problem of product availability and delivering a comprehensive synthetic library of Callyaerin derivatives in sufficient quantities. The lead structures CalA and CalB are active against *M. tb* while showing no cytotoxic effects, resulting in favorable selectivity ratios. CalA and CalB are active against *M. tb* XDR clinical isolates, implying that these compounds inhibit targets which are not affected by resistance mechanisms to clinical drugs in XDR strains. The gene Rv2113 was identified to be involved in the mechanism of resistance. Affinity enrichment using biotin-tagged Callyaerins and total cytosolic protein lysates revealed Hypoxic response protein 1 (HRP1) as an interaction partner. To gain further insides into the mode-of-action of Callyaerins, fluorescence microscopy using a dye-azide-tagged Callyaerin will be used to identify its intercellular location.

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Concise synthesis of natural products and kinase inhibitors by metal catalysis initiated One-Pot methodologies

Thomas J.J. Müller
Chair of Organic Chemistry, Institute of Organic Chemistry and Macromolecular Chemistry, Heinrich Heine University Düsseldorf, Germany.

Multi-component and domino reactions are efficient and effective methods in the rapid and diversity-oriented synthesis of heterocycles. Transition metal catalyzed multi-component sequences have considerably enhanced the synthetic tool box.[1] Most interestingly, in sequentially Pd-catalyzed processes[2] the same catalyst source is operative a second time without further catalyst addition. This one-pot methodological concept is most elegantly applied to concise syntheses of marine alkaloids and kinase inhibitors, the latter by applying a Masuda-borylation-Suzuki-arylation sequence[3] and alkynylation-based indolization.[4]

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Identification of new natural products with anti-microbial activity against Apicomplexa and multiresistant gram-negative rods (4MRGN)

Shabnam Shaneh Sazzadeh[1], Sarah Schmidt[1], Karin Buchholz[1], Peter Proksch[2], Klaus Pfeffer[1]
[1]Institute of Medical Microbiology and Hospital Hygiene, [2]Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Germany

Anti-microbial therapies have successfully treated infectious diseases. However, the recent occurrence of (multi-) resistant pathogens increases lethality and morbidity of infected patients. Apicomplexa like *Toxoplasma gondii (T. gondii)* also develop resistance against established treatments. Therefore, the need for new anti-microbial drugs is urgent. The primary aim of this project will be the identification of novel natural products with anti-microbial activities against *T. gondii* and multidrug resistant gram-negative rod-shaped bacteria (4MRGN), and the elucidation of their targets in pathogens in order to develop new leads for anti-microbial therapies.
Screening of natural products, which are able to inhibit *T. gondii* proliferation without being cytotoxic against HFF (human foreskin fibroblasts), is accomplished via Toxoplasma proliferation and MTT assays. To identify anti-4MRGN products microdilution assays are performed. Within a first round of screening, promising candidates could be detected. Furthermore, after performing the MTT assay none of the natural products demonstrate cytotoxicity against both cell lines, which were used in toxoplasma proliferation assay except Bionectriamide A.
In conclusion, a total of 300 new natural products and 30 derivatives thereof were analyzed against *T. gondii* (type I, BK strain and also type II, ME49 strain). Eleven products demonstrated anti-Toxoplasma activity and three of them have been selected for in depth analyses.

Diketopiperazine alkaloids from marine-derived fungus *Aspergillus* sp.

Chao-Yi Wang[1,2] , Ya-Hui Zhang[1,2], Xiao-Han Liu[1,2], Chang-Yun Wang[1,2*]
[1]Key Laboratory of Marine Drugs of Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China. [2]Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science and Technology, Qingdao 266071, China.

Diketopiperazine alkaloids are characterized by the condensation of tryptophan residue with another amino acid, such as proline and phenylalanine residue. This kind of alkaloids are widely distributed in endophytic fungi, such as *Aspergillus*, *Penicillium*, *Pestalotiopsis*, and *Chromocleista*, especially in the genera *Aspergillus* and *Penicillium*. In the course to investigate the alkaloids from the fungi *Aspergillus*, a series of new diketopiperazine alkaloids, especially prenylated indole alkaloids asperscleramides A−D with the bicyclo-[2.2.2]diazaoctane moiety, were isolated from one sponge-derived fungus *Aspergillus sclerotiorum* (GDST-2013-0501) and one gorgonian-derived fungus *Aspergillus* sp. (LA1104) collected from the South China Sea. The structures of these compounds were elucidated by extensive spectroscopic analyses, electronic circular dichroism (ECD) calculations and single-crystal X-ray diffraction. The structure of prenylated indole alkaloid asperscleramide D contains a rare fused-imine-containing pyrrolidin-3-one ring. Asperscleramide E represents the first prenylated indole alkaloid with ethylene oxide ring at the isopentenyl side chain. The DNA topoisomerase I (Topo I) inhibitory activities of the isolated compounds were all tested, and of these compounds, asperscleramide B and notoamide F displayed moderate activity with the MIC values of 100 and 50.0 μM.

Acknowledgements
This work was supported by the National Natural Science Foundation of China (Nos. 41830535; 81673350; U1706210), and the Taishan Scholars Program, China.

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Antibacterial and antiviral natural products from marine organisms collected from the South China Sea

Chang-Yun Wang[1,2,*], Chang-Lun Shao[1,2]
[1]Key Laboratory of Marine Drugs, the Ministry of Education of China, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China. [2]Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science and Technology, Qingdao 266071, China

Marine environment has proven to be a rich source to find bioactive natural products for drug discovery. Coral reefs are among the most productive marine ecosystems and are the source of a large group of structurally unique biosynthetic products. In recent decade, the South China Sea has become one of the hot spot for searching for new bioactive secondary metabolites from marine invertebrates and their symbiotic microorganisms. In recent years, we have initiated a program to discover bioactive natural products from marine invertebrates and their symbiotic microorganisms collected from the South China Sea. A series of antibacterial and antiviral natural products, including steroids, anthraquinones, alkaloids, and macrolides, have been isolated from sponges, soft corals, gorgonians, tunicates and their symbiotic fungi. For example, C-25 epimers of 26-acetoxy steroids obtained from the gorgonian *Echinogorgia rebekka* exhibited significant antiviral activity against respiratory syncytial virus (RSV). Anthraquinone derivatives from the coral-derived fungi *Alternaria* sp. and *Nigrospora* sp. exhibited potent antibacterial activities. Specifically, chlorinated benzophenone and piperazinedione alkaloids were isolated from soft coral-derived fungus *Pestalotiopsis* sp. The chlorinated benzophenone, (±)-pestalachloride D, showed antibacterial activity on *Escherichia coli*, while the piperazinediones exhibited strong antiviral activity against EV71 virus, 18-fold more potent than ribavirin. Our research revealed that the isolated natural products with antibacterial and antiviral activities showed the potential to be developed as marine lead compounds for drug discovery.

Acknowledgements
This work was supported by the National Natural Science Foundation of China (Nos. 41130858; 41322037; 41376145; 81673350), and the Taishan Scholars Program, China.

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Chemical diversity and biological activity of secondary metabolites from *Artemisia argyi* and its endophytic fungi

Xiao-Shan Shi, Bin-Gui Wang
Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071

Artemisia argyi, a typical medicinal plant distributed in Qichun of Hubei Province in the central China, is frequently used for the treatment of diseases such as eczema, hemorrhage, and inflammation. Multiple active metabolites including sesquiterpenes, triterpenes, flavonoids, and caffeoylquinic acid as well as essential oils were described from *A. argyi*. Endophytic fungi have been an essential source of the novel and bioactivity natural products, but the chemical constituents of endophytic fungi from *A. argyi* have not yet been reported. As part of our continuous research for new bioactive natural products from endophytic fungi, *Trichoderma koningiopsis* QA-3 and *Trichoderma virens* QA-8, which were obtained from the inner tissue of *A. argyi*, attracted our attention. The organic extract of the fungal culture exhibited antimicrobial activity against several marine-derived pathogens in our primary screening. Chemical investigations on the fungal culture resulted in the isolation and identification of 13 new polyketides *Trichoderma koningiopsis* QA-3 and 10 new sesquiterpenes from *Trichoderma virens* QA-8. The structures of these compounds were determined by detailed analysis of the spectroscopic data and the structures and absolute configurations of compounds were confirmed by a combination of X-ray crystal diffraction, specific optical rotations, CD spectroscopy, ECD calculation, and Mosher's methods. The isolated compounds were all assayed for their antimicrobial activities against human pathogen (*Escherichia coli*), marine-derived aquatic bacteria, and plant-pathogenic fungi.

Predicting orphan allosteric binding sites

Christopher Pfleger, Denis Schmidt, Susanne Hermans, Nicola Porta, **Holger Gohlke**
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-University, 40225 Düsseldorf, Germany.

A quantitative description of allostery is fundamental to an understanding of processes in living systems and of practical relevance when developing allosteric modulators. More recent models of allostery stress the influence of dynamics and large-scale conformational disorder. This provides the challenge from a computational point of view to develop an efficient methodological framework for analyzing, understanding, and predicting allostery in dynamic systems.
Here we present Constraint Network Analysis (CNA, web server: http://cpclab.uni-duesseldorf.de/cna/) as such a framework. CNA applies concepts grounded in rigidity theory to analyze biomolecular flexibility[1]. We applied CNA in terms of a perturbation approach to gain structure-based insights into allosteric signaling and coupling in dynamic proteins[2]. Our results demonstrate that the approach can describe quantitatively allostery in dynamic systems. Finally, we extended our approach to allow for the identification of sites in proteins that are allosterically coupled even in cases when no allosteric modulator is known yet. This makes CNA an interesting tool in the context of target identification and validation.

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Virtual screening-based identification and Molecular Dynamics study of Nisin resistance protein (NSR) lead inhibitors

Nicola Porta[1], Julia Zaschke-Kriesche[2], Benedikt Frieg[1,3], Sander H.J. Smits[2] and Holger Gohlke[1,3]

[1.] Institute for Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. [2.] Institute of Biochemistry, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. [3.] John von Neumann Institute for Computing, Jülich Supercomputing Centre, Institute for Complex Systems-Structural Biochemistry (ICS-6), Forschungszentrum Jülich GmbH, Jülich, Germany.

Lantibiotics are potent broad-range antimicrobial peptides. They are attractive candidates as antiinfective drugs and food preservatives due to their high activity and stability. However, in several human pathogenic strains, resistance has been reported, limiting their usefulness. In particular, a natural immunity to nisin, the most prominent lantibiotic, is mainly attributed to the Nisin Resistance Protein (NSR). NSR has been shown to inactivate nisin by cleaving the last six C-terminal residues. Here, virtual screening on a library of ~10 million commercially available compounds guided the identification of molecules able to interfere with NSR activity. Combining shape matching, using nisin as query, with molecular docking into NSR binding site allowed the selection of ~25 top scoring ligands that were further characterized. We reveal that two of them significantly reduce NSR activity and make *L. lactis* bacteria expressing NSR sensitive to nisin in a concentration-dependent manner, as shown by the cleavage efficiency assay and by the growth inhibition assay, respectively. Additionally, molecular dynamics simulations allow us to capture the binding of small molecules diffusing from solvent to the NSR binding region. This description of molecular action is of utmost importance to understand what are the requirements for activity and to support our lead optimization endeavors.

Resistance against lantibiotic mediated by specific operon detected in human pathogens

Sander H.J. Smits
Institute of Biochemistry and Center for Structural Studies, Heinrich Heine University Düsseldorf, Germany

The need for new antibiotic compounds is raising. Antimicrobial peptides and especially lantibiotics are excellent candidates to fulfill this function. Lantibiotics contain unusual amino acids and lanthionine rings, which ensure their high stability and high potency. They are active in the nanomolar range and exhibit two main modes of action mainly against Gram-positive bacteria: Binding to the precursor of lipid II as well as pore formation within the bacterial membrane, which leads to immediate cell death. Commercial usage is, however hampered by the presence of genes in human pathogenic strains which, when expressed, confer resistance against such lantibiotics.
The human pathogen *Streptococcus agalactiae* COH1, is for example resistant against lantibiotics due to the nsr-operon (Khosa et al. 2013) encoding a two-component system NsrRK, the nisin resistance protein (NSR) (Khosa et al. 2016) and an BceAB type ABC transporter NsrFP (Reiners et al. 2017). Interestingly, the genes appear to be evolutionary conserved in human pathogenic bacteria.

Here, I will present our recent research on the topic of lantibiotic resistance highlighting the mechanism of the NSR protein as well the two component system. Furthermore, a new approach to express and characterize lantibiotic in general will be highlighted.

S. Khosa et. al (2013) Biological chemistry 394, 1543-1549 394, 1543-1549
S. Khosa et. al (2016) Scientific Reports, 6, 18679
J. Reiners (2017) Frontiers in Microbiology doi: 10.3389/fmicb.2017.01643

Functional and structural studies of the Nisin Resistance Protein NSR of *Streptococcus agalactiae*

Julia Zaschke-Kriesche[1], Nicola Porta[2], Lara Behrmann[1], Holger Gohlke[2,3] and Sander H.J. Smits[1]

[1]Institute of Biochemistry and Center for Structural Studies, Heinrich Heine University Düsseldorf, Germany. [2]Institute for Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. [3]John von Neumann Institute for Computing, Jülich Supercomputing Centre, Institute for Complex Systems-Structural Biochemistry (ICS-6), Forschungszentrum Jülich GmbH, Jülich, Germany.

The antimicrobial peptide nisin contains 34 amino acids and is produced by some *Lactococcus lactis* strains. Nisin belongs to the lantibiotic subfamily and displays high antimicrobial activity against mainly Gram-positive bacteria. The human pathogen *Streptococcus agalactiae*, however is resistant against nisin due to the upregulation of membrane associated proteins of the *nsr*-operon (1). These are the ABC-transporter NsrFP and the nisin resistance protein SaNSR. Latter is a serine protease, which inactivates nisin by cleaving off the last six amino acids. We solved the X-ray structure of *Sa*NSR, which revealed that NSR specifically recognizes nisin by the last two lanthionine-rings (2).
The goal of this study is to overcome the lantibiotic-resistance in human pathogens using nisin as a model system. We used shape matching and molecular docking to screen over 10 million compounds suitable to act as inhibitors. The identified compounds were subjected to *in vivo* and *in vitro* assays to identify their ability to specifically inhibit *Sa*NSR.
Here, we present the functional characterization of *Sa*NSR as well as the first subset of compounds, which can be used to bypass lantibiotic resistance in human pathogens allowing displaying the full potential of these peptides.

1) S. Khosa et. al (2013) Biological chemistry 394, 1543-1549
2) S. Khosa et. al (2016) Scientific Reports, 6, 18679

Chemoenzymatic natural product synthesis

Andreas S. Klein,[1] Andreas Domröse,[2] Hannah Brass,[1] Anita Loeschcke,[2] Thomas Classen,[3] David P. Klebl,[1] Tim Moritz Weber,[1] Thomas Drepper,[2] Karl-Erich Jaeger,[2,3] and **Jörg Pietruszka**[1,3]*

[1]*Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf located at Forschungszentrum Jülich, Stetternicher Forst, 52426 Jülich*

[2]*Institute of Molecular Enzyme Technology, Heinrich Heine University Düsseldorf located at Forschungszentrum Jülich, Stetternicher Forst, 52426 Jülich*

[3]*IBG1: Biotechnology, Forschungszentrum Jülich, 52428 Jülich*

Prodiginines are a class of microbial secondary metabolites produced by different Gram-positive and –negative bacteria such as *Streptomyces coelicolor* and *Serratia marcescens*. Prodiginines exhibit various pharmacological relevant properties including antibiotic activities against various pathogens such as *Salmonella typhi*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[1] The red-pigmented tripyrrol prodigiosin is naturally synthesized from amino acid and acetate building blocks. Since *S. marcescens* is an opportunistic pathogen that accumulates prodigiosin in low amounts, the development of alternative strategies for an efficient synthesis independent of the original producer is of great interest.

The prodigiosin gene cluster from *S. marcescens* has been integrated into the chromosome of the GRAS certified bacterium Pseudomonas putida accumulating prodigiosin at substantial levels. We will present our recent findings for prodigiosin extraction, purification and quantification, as well as an approach towards natural product derivatives and their physiological properties.[2]

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Towards the total synthesis of heterobiaryl natural products and their derivatives

Julian Greb[1] and Jörg Pietruszka[1,2]
[1]Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, located at Forschungszentrum Jülich, Stetternicher Forst, 52426 Jülich; [2]IBG-1: Biotechnology, Forschungszentrum Jülich, 52428 Jülich

As multi drug resistance (MDR) of cancer cells and pathogens has become an increasingly pressing problem for the pharmaceutical treatment of diseases in the recent years, there is a growing demand for novel drug-like molecules and lead structures. Therefore, modern natural product synthesis has partly shifted its focus away from a 'classical', purely target-oriented approach towards more diversity-oriented strategies[1]. Among the broad variety of bioactive natural products – from which medicinal chemists draw their inspiration – dimeric heterobiaryls exhibit remarkable bioactivities as well as an intriguing chemistry and structures. Some prominent representatives are the tetrahydroxanthone dimers[2] Secalonic acid D[3] and Phomoxanthone A[4] or Gonytolide A[5], which belongs to the closely related class of chromanone lactone dimers. Here, we will present our recent findings towards the synthesis of this class of complex compounds based on the use of common precursors and key intermediates, which should enable a rapid diversity generation.

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Using photo-affinity labeling approach for the target identification of two marine bioactive compounds

Jianrong Liu
School of Pharmaceutical Science, Peking University

The protein target identification of experimental compounds now represents a major bottleneck in the drug discovery pipeline. With the protein targets of new lead compounds in hand, the process of lead compound optimization can be much more purposeful and efficient. It is therefore to rapidly identify the targets of developed lead compounds in the early stage of the drug discovery. Various techniques have been developed to study this specific proteins. Photo-affinity labeling (PAL) approach is one of the most powerful strategies in this application. It contains a photo-active group that can be activated by UV irradiation to generate a reactive species that will establish a covalent bond to the protein targets. Two examples of this approach applied on marine bioactive compounds are presented. These include the design, organic synthesis of their corresponding photo-affinity probes; the bioactivity tests of the newly synthesized probes and their protein target identification process.

Diversity-oriented One-pot synthesis of novel active agents against therapy resistant tumors and infections

Daniel Drießen, Thomas J. J. Müller
Chair of Organic Chemistry, Institute of Organic Chemistry and Macromolecular Chemistry, Heinrich Heine University Düsseldorf, Germany.

A variety of marine alkaloids, such as meridianins[1] and variolins,[2] consist of an indole or a 7-azaindole core. Together with a 2-aminopyridinyl moiety in 3-position, this structural element becomes a lead structure for the inhibition of kinases. In principle, 3-heteroaryl substituted 7-azaindoles are potent hinge binders in kinases.[3] Simple synthetic access to these class of substances is therefore of great importance. The Masuda-borylation-Suzuki-coupling sequence is a reliable methodology for easily accessing a broad spectrum of these potential novel active agents in a one-pot fashion.[4] Moreover, a highly diversity-oriented synthesis by simply changing the halides can be readily achieved.

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Establishing the autophagy-inducing protein complexes as targets for cancer therapy

Björn Stork
Institute of Molecular Medicine I, University Hospital Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf

(Macro-)Autophagy is an intracellular degradation process mediating the clearance of misfolded or damaged proteins, protein aggregates, or entire organelles. This process is conserved from yeast to higher eukaryotes including mammals, and autophagy is essential for functional metabolism and cell integrity. Autophagy is executed by a set of autophagy-related (ATG) proteins supported by several non-ATG proteins. The initiation of this process is mediated by the ULK1 protein kinase complex and the class III PtdIns3K lipid kinase complex. As a cyto-protective stress response, autophagy supports the survival of tumor cells under nutrient-limited conditions or upon treatment with diverse anti-cancer regimens such as hormonal deprivation, chemotherapy, or radiation. Furthermore, it has been shown that autophagic processes within the tumor microenvironment can be similarly tumor-supporting. There are currently several clinical trials aiming at the inhibition of autophagy. However, they mostly rely on the non-autophagy selective compounds chloroquine or hydroxychloroquine, emphasizing the need for more selective approaches. In our group, we are aiming at establishing the two autophagy-inducing complexes as therapeutic targets for cancer treatment. Here, a brief overview of our approaches will be presented.

Identification of autophagy-modulating natural products and derivatives for the elimination of therapy-resistant tumor cells

Jana Deitersen, David Schlütermann, Fabian Stuhldreier, Pia Liebfried, Philip Böhler, Niklas Berleth, Wenxian Wu, Xiaojing Wang, Björn Stork
Institute of Molecular Medicine I, University Hospital Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf

Autophagy is an intracellular degradation process involved in cellular homeostasis and survival. Its dysregulation has been linked to human diseases including cancer, cardiomyopathy or neurodegeneration. Macroautophagy (hereafter referred to as autophagy) involves sequestration and lysosomal digest of various cellular components. While this recycling has a tumor-preventing effect in healthy cells, it also serves as source of energy especially benefitting starving cells e.g. in hypoxic cancer tissues. Therefore, compounds that modulate autophagy like the approved mTOR inhibitor everolimus (Afinitor®) have a huge chemotherapeutical potential. Nature is a nearly inexhaustible source for new compounds and future drugs.
Therefore, we screened 300 natural compounds for their effect on autophagy and identified promising autophagy-modulating compounds. These are now being further evaluated for sensitization of cisplatin-resistant bladder cancer cells to chemotherapy and the characterization of their molecular pathway and target.

Chemical diversity of terpenoids from the deep sea-derived fungus *Aspergillus wentii* SD-310

Xin Li, Xiao-Ming Li, Xiao-Dong Li, Bin-Gui Wang*

Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071, China

Terpenoids are a family of structurally abundant and biologically active natural products, which are often encountered among plants and fungi. As part of our ongoing efforts to discover bioactive metabolites from marine-derived fungi, we recently focused our attention on *Aspergillus wentii* SD-310, a fungal strain obtained from a deep sea sediment sample. To increase the structural diversity of secondary metabolites from SD-310, attempts to cultivate the fungus in various media and conditions were performed. Interestingly, the fungus was found to produce a series of tetranorlabdane diterpenoids in static cultivation, while a number of 20-nor-isopimarane diterpenoids as well as isopimarane diterpenoids were discovered in shaking cultivation. Among them, asperethers A–E are 20-nor-isopimarane diterpenoids having a 14,16-cyclic ether unit and possessing a unique 6/6/6/5 tetracyclic skeleton, which have so far not been described for this class of diterpenoids. In addition, wentinoid A possesses a unique 20-acetal and a 7,20-oxa-bridged functionality, while wentinoid B contains an unusual 8,20-lactone-bridged scaffold. The structures of these compounds were established on the basis of detailed interpretation of NMR and mass spectroscopic data, and their relative and absolute configurations were confirmed by NOESY data and X-ray crystallographic analysis, as well as by TDDFT calculations of their ECD spectra. Some of these compounds showed cytotoxic activities and inhibitory activities against plant-pathogenic fungi.

Expanding the metabolic profile of the endophytic fungus *Humicola grisea*

Nam Michael Tran-Cong[a] ,Haiqian Yu[a], Fabian Stuhldreier[b] , Werner E.G. Müller[c], Sebastian Wesselborg[b] Wenhan Lin[d], Zhen Liu[a], Peter Proksch[a]

[a]Institute of Pharmaceutical Biology and Biotechnology, HeinrichHeine University Düsseldorf, 40225 Düsseldorf, Germany; [b]Institute of Molecular Medicine I, Heinrich Heine University, Universitätsstraße 1, 40225 Düsseldorf, Germany; [c]Institute of Physiological Chemistry, Johannes Gutenberg University Mainz, 55128 Mainz, Germany; [d]State Key Laboratory of Natural and Biomimetic Drugs, Peking University, 100191 China

The term OSMAC (**O**ne **S**train **MA**ny **C**ompounds), first introduced by Zeeck *et al.* describes a strategy to induce microbial natural product biosynthesis by employing different cultivation conditions. This method as well as fungal bacterial co-cultivation can be used to diversify fungal secondary metabolite profiles, as a change in cultivation conditions may activate silent biosynthetic gene clusters, thus leading to the accumulation of previously unknown natural products.

In this study we investigated natural products of the fungal endophyte *Humicola grisea* (Cheatomiaceae) isolated from roots of the Vietnamese medicinal plant *Houtuynia cordata*. The EtOAc extract of this fungus when grown on solid rice medium yielded eleven compounds which included 5 new compounds. Two further compounds which were not present in axenic culture were isolated when the fungus was co-cultivated with *Bacillus subtilis* whereas changes of the media yielded five additional compounds.

The structures of all metabolites were elucidated by MS/HRMS, NMR and comparison with the literature. All compounds were submitted for cytotoxicity assays. Three new compounds, one of them isolated from the axenic fungal culture and two compounds from the OSMAC experiments were active against a mouse lymphoma cell line with IC_{50} values ranging from 0.155 to 4.06 µM. Two of these compounds also exhibited activity against Jurkat and Ramos cells with IC50 values ranging from 6.0 to 30 µM.

Probiotics inspired antibiotics to target superbugs

Kui Zhu
Beijing Advanced Innovation Center for Food Nutrition and Human Health, National Center for Veterinary Drug Safety Evaluation, College of Veterinary Medicine, China Agricultural University, Yuanmingyuan West Road No.2, Beijing, 100193, China

Rapid emergence and dissemination of multi-drug resistant (MDR) pathogens pose a serious global threat to health care. New strategies and antibacterial compounds are urgently needed to combat bacteria associated infections. Probiotic microbes conferring health benefits to the hosts have attracted great attention and are widely applied nowadays. However, the underlying mechanism of most probiotic strains remains unclear. We characterized a novel cyclic lipopeptide from probiotic *Bacillus subtilis* CAU21, which shows broad antibacterial activity against MDR Gram-positive pathogens including notorious methicillin-resistant *Staphylococcus aureus* (MRSA). Furthermore, we synthesized a library of derivatives to investigate the structure-activity relationship of bacaucin. Interestingly, bacaucin-1a, a rationally engineered ring-opened, non-cationic heptapeptide, exhibits selective antibacterial activity against 100 MRSA isolates from both human and animal origins. Bacaucin-1a was efficient to prevent MRSA associated infections in both *in vitro* and *in vivo* models with unique mode of action. Our findings provide a potential therapeutic to address the recent prevalence of infections caused by MDR bacterial pathogens worldwide.

Diversified metabolites from marine derived fungi

Bin-Gui Wang
Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071

China has a rich source of marine organisms covering from temperate to tropical zones. We focused our interests in recent years to search for diversified bioactive natural products from marine-derived endophytic fungi. As a result, a wide range of natural occurring compounds including alkaloids, quinones, terpenoids as well as other kinds of compounds have been isolated and identified. These compounds displayed various biological activities. Among them, tetranorditerpenoids isolated from algal-derived endophytic *Aspergillus wentii* EN-48 displayed potent cytotoxicity against eight tumor cell lines. Further experiments indicated the *in vivo* activity against human cell lung carcinoma cell line (NCI-H460) and human small cell lung carcinoma cell line (NCI-H446). The antitumor activity, both *in vitro* and *in vivo*, the toxic experiment and the *in vitro* metabolism as well as the mode of action will be presented in the presentation.

From selectivity to targeted promiscuity

Holger Stark
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Germany

In our research group we have focused on various chemical structures from lipid modulators to neurotransmitter agonists as well as antagonists. With numerous natural and endogenous lead structures, it was possible to develop new leads and to optimize different compound classes having various structural motifs with different targets.
These optimizations have been performed on inflammatory targets as COX-I/II and 5-lipoxygenase in the arachidonic pathway [1], but also at different key enzymes and receptors on sphingolipid signalling [2-4]. In the field of neurotransmitters, it was possible to develop selective ligands with altered efficacies on different dopamine and histamine receptor subtypes [5,6].
Numerous diseases have more than one molecular target. Addressing only one target does not give the optimal therapeutic response. Therefore, we have put one focus on multitargeting compounds [7-9]. In a recent approach, we combined histamine H3 receptor antagonist, monoaminoxidases B and A inhibition with inhibition of acetylcholine esterase and butyrylcholine esterase inhibition. This multitargeting approach of design-in of different receptors and enzymes was combined with a design-out at off-targets leading to contilisant as small molecule with a unique profile as potential compound against Alzheimer´s disease [10].

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Natural compounds and small molecules targeting the histamine H_4 receptor

Annika Frank and Holger Stark*
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Germany

The fourth histamine receptor (H_4R) is a G-protein-coupled receptor, playing a key role in chemotaxis, inflammation and autoimmune disorders. Based on its influence on cell proliferation and immune modulation it is a promising target against several cancer types (e.g. recently on breast cancer [1] and on Leydig-cell tumours [2]). Therefore, the demand for novel chemical scaffolds is on the rise.
As natural products are a valued source for therapeutic agents, the evaluation of natural compounds and their derivatives delivers new chemical entities for H_4R ligands. In this project, we evaluate the activities of natural compounds and small molecules at the hH_4R in search for novel ligands. Pyrrolo[2,3-d]pyrimidine derivatives are present in several marine organisms [3] and are promising scaffolds for a wide application field. The evaluation of twelve novel pyrrolo[2,3-d]pyrimidines showed promising affinities at histamine H_3 and H_4 receptor subtypes, with preference for the H_3 receptor [4].
As spices like curcuma are easier to obtain than compounds from marine organisms, it is a popular traditional remedy against various conditions, although its mode of action remains incomplete. By evaluating the extracted compounds of curcumin, we found novel potential ligands at the H_4R (K_i values between 0.5 µg/mL and 4.5 µg/mL), thereby elucidating curcumins mode of action and emphasizing the role of extracts in traditional phytomedicine [5].
In conclusion, our research traces the pharmacodynamic of natural compounds and aids in finding novel scaffolds for a current target against cancer diseases.

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Plasmacytoid dendritic cells and type I interferon as immunomodulators in infectious diseases

Stefanie Scheu and Lisa Richter
Institute of Medical Microbiology and Hospital Hygiene, University of Duesseldorf, Germany

Type I interferons (IFNs), a cytokine family consisting of IFNβ and multiple subtypes of IFNα, were originally identified on the basis of their antiviral activity but are known today to modulate the immune response in multiple ways. It is generally assumed that plasmacytoid dendritic cells (pDCs) are efficient producers of high amounts of type I IFN in viral infections. Using an IFNβ/YFP reporter mouse we recently defined the source of IFNβ in the spleen during Cytomegalovirus infection as a distinct subset of pDCs. Challenging the current dogma, IFNβ was produced only by 10% of all pDCs. Transcriptome analysis revealed that IFNβ-producing pDCs exhibit a differential gene expression signature consisting mainly of genes involved in immune modulation with a bias toward T cell recruitment and activation when compared with non IFNβ-producing pDCs. Thus, IFNβ-producing pDCs constitute a specialized pDC subpopulation coordinating cellular immune responses within secondary lymphoid tissues. Currently functional selected genes differentially expressed in IFNβ-producing pDCs are underway to define novel immune regulatory and effector functions of specialized pDC subpopulations.
In a screening approach we are further analyzing the influence of Histone-Deacetylase Inhibitors on the expression of type I IFN in pDCs as our experiments indicate for the first time an influence of these epigenetic regulation factors on the production of type I IFN in pDCs.

Identifying immunological properties of natural products for the treatment of chemoresistant tumors and bacterial pathogens

Lisa Richter[1], Peter Proksch[2], Stefanie Scheu[1]
[1]Institute of Medical Microbiology and Hospital Hygiene, University of Düsseldorf, Germany
[2]Institute of Pharmaceutical Biology and Biotechnology, University of Düsseldorf, Germany

The most abundant human diseases worldwide include cancer and bacterial infections. To overcome the development of resistances against cytostatics and antibiotics, there is a rising need to find new drugs. Natural products comprise many highly bioactive molecules inspiring medical research. We are looking for novel compounds that modulate immune effector functions and additionally target tumors and pathogens, thus reducing the risk of resistances.
A library with 240 natural products derived from endophytic fungi and marine sponges undergoes different screenings to identify promising compounds. We have already found 41 natural products that are non-toxic to immune cells but simultaneously toxic to tumor cells or pathogens. To determine immunostimulatory characteristics we are currently using an IL-12p40 fluorescence reporter mouse line to test selected natural products for their ability to induce or enhance expression of the immunostimulatory cytokine IL-12 in dendritic cells or macrophages. The thus identified immune activating compounds will be further interrogated in T cell activation assays for their impact on T cell priming by dendritic cells. Moreover, the molecular mechanisms underlying the immunostimulatory capacity of the defined natural products will be elucidated. Promising multifunctional, immune activating compounds will further be biochemically optimized for immunomodulatory effectivity and tested in *in vivo* tumor and infection mouse models.

Identifying bioactive natural compounds from mangrove-derived endophytic fungi

Ling-Hong Meng, Xiao-Ming Li, Bin-Gui Wang
Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071

Marine natural products, characteristics of unique chemical structure, various potent biological activities and drug-like properties, have become one of the most important resources of novel lead compounds for the critical diseases, and played important roles on the development of new drugs. This presentation will focus on the discovery of unprecedented antitumor sulfur-containing compounds such as spirobrocazines A-C, brocazines A-G, penicibrocazines A-E from mangrove-derived endophytic fungus *Penicillium brocae* MA-231 and sumalarins A–C from *P. sumatrense* MA-92, which obtained from the mangrove plant *Lumnitzera racemosa*. The antitumor sulfur-containing compounds were affordable via either traditional or untraditional cultivation strategies. With structures established by NMR spectroscopic, TDDFT-ECD calculations, and X-ray diffraction analyses, the structure-activity relationships (SARs) and biosynthetic pathways of the sulfur-containing compounds were discussed as well.

Targeting mechanisms of DNA damage response (DDR) to overcome anticancer drug resistance of tumor cells

Jana van Stuijvenberg, Gerhard Fritz
Institute of Toxicology, Medical Faculty, Heinrich-Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany

The major therapeutic target of conventional anticancer therapeutics (cAT) is the genomic DNA of tumor cells. In consequence of DNA damage, a complex stress response program, named DNA damage response (DDR), gets activated. The PI3-like protein kinases ATM and ATR are key regulators of the DDR because they ensure the coordinated regulation of DNA repair, activation of cell cycle checkpoints and apoptosis. The aim of the study is to identify natural compounds derived from endophytic fungi and marine sponges that interfere with the DDR, thereby re-sensitizing resistant tumor cells to cAT. To investigate the cytotoxic and genotoxic potency of 300 different natural compounds themselves or in combination with cAT (e.g. Cisplatin), cell viability was analyzed and the activation status of the DDR was examined by measuring the ATM/ATR-catalyzed phosphorylation of histone H2AX (γH2AX) using a self-established 96-well plate array. Some of the compounds (e.g. 5 - epi-Ilimaquinone, Fusarielin J) were shown to be toxic in tumor cells and to activate the DDR themselves and/or to promote the DDR if used in combination with cAT. The DDR modifying natural compounds will be further characterized regarding (i) their molecular mode of action and (ii) their impact on the survival of cAT-treated tumor cells of different origin.

The deletion of a histone deacetylase gene (PMG11_08486) leads to secondary metabolic changes of penicillic acid and brasiliamide in *Penicillium brasilianum*

Bochuan Yuan, Jianping Zhang, Xin Guan, Dong Liu, Wenhan Lin*
State Key Laboratory of Natural and Biomimetic Drugs, Peking University

Epigenetic repression is an important method to activate silent genes in fungi, while histone deacetylase gene plays key role in epigenetic repression. In this work, a histone deacetylase gene (*PMG11_08486*) was selected from all epigenetic regulators of a marine-derived *Penicillium brasilianum* by Neighbor-Joining clustering, to uncover gene function relevant to the production of secondary metabolism. A mutant strain with *PMG11_08486* deletion was generated by CRISPR/Cas9 method and PCR verification, showing a 2228bp fragment deletion occurred in *PMG11_08486* CDS. HPLC detection showed that the mutant strain significantly changed the metabolic profile in comparison with that of the wild type, in which the mutant strain produced a new compound (brasiliamide G) but absent penicillic acid that produced by the wide type strain. Quantitative real-time PCR revealed that the synthetic gene (type II PKS) of orsellinic acid, the precursor substance of penicillic acid, was inactivated. Feeding radioactive phenylalanine (2C-^{13}C) to the mutant *P. brasilianum* indicated that brasiliamide was derived from a phenylalanine and a tyrosine by NRPS condensation.

Cancer-specific pro-apoptotic effects of the mycotoxin viriditoxin

Fabian Stuhldreier[#], Yang Liu[§], Paul Jäger[&], Stefanie Geyh[&], Niklas Berleth[#], Philip Böhler[#], Jana Deitersen[#], Maria Jose Mendiburo[#], David Schlütermann[#], Wenxian Wu[#], Rainer Haas[&], Peter Proksch[§], Björn Stork[#], Sebastian Wesselborg[#]

[#]Institute of Molecular Medicine I, Heinrich Heine University Duesseldorf, Germany
[§]Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Duesseldorf, Germany
[&]Department of Haematology, Oncology and Clinical Immunology, University Hospital Duesseldorf, Germany

We identified viriditoxin (VT), a mycotoxin isolated from *Paecilomyces variotii* fungus, as a highly potent inducer of apoptosis in human leukemia and lymphoma cell lines with EC_{50} values in the nanomolar range. Subsequently, we analyzed VT in hematopoietic stem and progenitor cells (HSPC), derived from healthy donors, in order to examine adverse side effects on untransformed cells and thus characterizing its usefulness as a lead compound for the development of new drugs in the therapy of hemato-oncological diseases. Administration of high doses, which strongly induced apoptotic cell death in different leukemia and lymphoma cell lines, did not affect the viability of HSPC, indicating minor side effects. Further experiments showed that the distinct cytotoxicity of VT in leukemia and lymphoma cells is caused by impairment of mitochondrial function. Treatment with VT leads to breakdown of the mitochondrial membrane potential in a caspase-independent manner. Moreover OPA1, a key regulator of mitochondrial fusion, immediately gets cleaved upon application of VT. Finally, we could show that VT blocks cellular respiration indicated by decreased O_2 consumption and causes a reduction of cellular ATP levels.

Dxr as target for anti-infective drug discovery: Synthesis, antiplasmodial properties and structural biology of reverse fosmidomycin derivatives

C. Lienau[a], A. Kunfermann[b], S. Konzuch[a], T. Umeda[c], J. Held[d], U. Riederer[e], B. Illarionov[f], T. Gräwert[f], C. T. Behrendt[a], K. Brücher[a], A. Bacher[b], N. Tanaka[c], M. Groll[b], B. Mordmüller[d], M. Fischer[f], S. Wittlin[g], **Thomas Kurz [a,*]**

[a,*]Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany,
[b]Center for Integrated Protein Science Munich, Technical University of Munich, Lichtenbergstr. 4, 85747 Garching, Germany,
[c]School of Pharmacy, Showa University, Tokyo 142-8555, Japan,
[d]Institute of Tropical Medicine, Eberhard Karls University Tübingen, Wilhelmstr. 27, 72074 Tübingen, Germany,
[e]Hamburg School of Food Science, University of Hamburg, Grindelallee 117, 20146 Hamburg, Germany,
[f]Institute of Pharmacy, University of Hamburg, Bundesstraße 45, 20146 Hamburg, Germany,
[g]Swiss Tropical and Public Health Institute, Socinstr. 57, University of Basel, 4051 Basel, Switzerland.

Antimicrobial resistance remains an unresolved global health problem and endangers the effective prevention and treatment of an increasing number of infectious diseases.[1-5] A promising approach for the development of novel anti-infective drugs is the inhibition of the non-mevalonate isoprenoid biosynthesis (MEP pathway). The natural product fosmidomycin, currently undergoing phase II clinical trials in combination with piperaquine, blocks the MEP pathway by inhibiting 1-deoxy-d-xylulose-5-phosphate reductoisomerase (Dxr, IspC). Dxr is the first committed enzyme of the MEP pathway that is essential in *Plasmodium spp*. and various other pathogenic microorganism but is absent in the human host. While fosmidomycin's mechanism of action and its toxicity profile are favourable, the antiplasmodial and pharmacokinetic properties of are improvable. We report the synthesis and antiplasmodial properties of reverse fosmidomycin analogues as well as kinetic and crystallographic evidence for their mode of action.[1-5]

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Synthesis and biological evaluation of novel Panobinostat derivatives

Marc Pflieger
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstr. 1, 40225 Düsseldorf, Germany

Cancer is one of the main reason of fatality in industrial countries, despite of improving therapeutic options.[1] Besides the therapeutical approach to target chemoresistance directly, addressing the aberrant gene expression machinery remains a valuable anticancer strategy. Therefore, targeting epigenetic processes in cells that underwent malignant transformation becomes increasingly important in cancer treatment. [2]
The defective silencing of tumour suppressor genes by hypoacetylation of histones is commonly observed in various cancer cell lines, caused by an overexpression of histone deacetylases (HDACs). Such a hypoacetylation results in a more condensed chromatin structure which impedes the accessibility of the transcriptional machinery and thereby a decreased expression of tumour suppressor genes. Inhibiting HDACs can thereby reinstate the expression of tumour suppressor genes. [3]
Panobinostat, a pan inhibitor, was approved by the FDA in 2015 for the treatment of multiple myeloma. This highly potent HDAC inhibitor exhibits an indol based CAP group, an amino connecting unit (CU), a *p*-methyl cinnamyl linker and a hydroxamate as zinc binding group (ZBG). One potential optimisation might be the introduction of an hydroxylamine moiety as CU, as it has been shown that compounds exhibiting this structural motif can overcome cisplatin chemoresistance.[4,5] In this project, the influence of the CU and novel CAP groups were evaluated in respect to potency and isoform preference.
A synthetic strategy was developed to introduce the hydroxylamine moiety into cinnamyl hydroxamate based HDAC inhibitors exhibiting an alkoxyurea or an alkoxyamide. The obtained compounds were biologically evaluated in respect to isoform preference and cytotoxicity.

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Molecular mechanism of S-nitrosoglutathione on ultrastructure of pancreatic islet beta cells in db/db mice

Junjie Jiang[1], Kaijie Zhang[1], Xin Huang[2]*, **Yijia Lou**[1]*
[1]Institute of Pharmacology and Toxicology, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China [2]Cardiovascular Key Laboratory of Zhejiang Province, The 2nd Affiliated Hospital, Hangzhou 310009, China

Type 2 diabetes mellitus (T2DM) model, *db/db* mice, shows the symptoms of high weight, hyperglycemia and hyperinsulinemia. Nitric oxide can promote the translocation of glucose transporter 4 in somatic cells, thereby promoting the use of glucose in *db/db* mice. Here we explore the ultrastructural features and molecular mechanisms of pancreatic beta cell in *db/db* mice, and the possible effects of nitric oxide donor *S*-nitrosoglutathione (GSNO) on ultrastructure of beta cells. Both *db/db* mice and BKS wild mice (as controls) treated with saline or GSNO by intraperitoneal injection, starting from 8-week old to 12-week old or 16-week old. Blood glucose and insulin were measured. The tissue evaluation included the ultrastructure, micromorphological features, and related molecular biological changes. At 12 weeks old, endoplasmic reticulum enlarged. Mitochondrial crista disappeared, and the "plasma membrane-endoplasmic reticulum-mitochondrial axis" disrupted in beta cells of *db/db* mice. At 16 weeks old, GSNO significantly improve the deficiency of the plasma membrane-endoplasmic reticulum-mitochondrial axis juxtaposition structure, and the level of blood insulin is significantly higher than that in control. But it does not decrease hyperglycemia and body weight. The molecular mechanism might be related to the amplification of Ca^{2+} signal by regulating RyR2 and p-CaMKII. It is suggested that the plasma-endoplasmic reticulum-mitochondrial axis of islet beta cells is damaged during the middle and late growth period of *db/db* mice. GSNO can protect the ultrastructure from injury and delay the outcome of insulin-reducing point, but can not improve the insulin resistance.
* Corresponding authors. This work was supported by the National Natural Sciences Foundation of China (No. 81573513).

Application of high-content imaging for the study of apoptosis induction by novel anti-cancer agents

Chenyin Wang, Matthias U. Kassack
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-University Duesseldorf, Germany

Cancer is the second leading cause of death worldwide. Unlike normal cells, cancer cells often fail to start a process known as programmed cell death or apoptosis and grow out of control. Therefore, re-establishment of apoptosis induction is an important strategy of anti-cancer drug development. High content imaging offers a plethora of assays for the study of apoptosis. Generally, induction of apoptosis is mediated by intrinsic and/or extrinsic pathways. The extrinsic apoptosis pathway is triggered by activation of death receptors finally activating caspase 3. The intrinsic pathway is initiated by mitochondrial damage and subsequent release of cytochrome C. In this study, cell-based high-content imaging assays were performed using the Thermo Fisher ArrayScan XTI platform to investigate apoptosis induction in human tumor cell lines upon treatment with novel anti-cancer compounds. Assays included mitochondrial membrane potential, cytochrome C release, activation of caspase 3, and cell viability. Results of these assays provide insight into the possible mechanism of cell death induced by the anti-cancer compounds.

The genome mining and synthetic biology of diterpenoids from marine and plant endophytic bacteria

Xiaoxu Sun, Baiying Xing, Yuanjie Ge, Ming Ma, **Donghui Yang**
School of Pharmaceutical Sciences, Peking University

Diterpenoids are a family of structurally complex natural products with diverse chemical skeletons and broad therapeutic applications. Plants and fungi provide the major source of these natural products and present a rich reservoir of potentially pharmaceuticals, yet the cloning and engineering of diterpenoid biosynthetic pathways in these organisms remain challenging. Bacteria are emerging as prolific producers of diterpenoid natural products, and the functional characterization of bacterial diterpene synthases is poised to make significant contributions to our understanding of terpenoid biosynthesis. We have constructed the marine and plant endophytic bacteria library and their genomic DNA library (3000 strains up to now), and carried out the screening of potential diterpenoid-producing strains by using genome mining methods. The discovery of new diterpenoids from the "positive" strains, and the heterologous expression of whole diterpenoid biosynthetic gene clusters or individual diterpenoid synthases in heterologous hosts are ongoing.

Poster Abstracts

Development of class IIa HDAC inhibitors

Yodita Asfaha and Thomas Kurz
Institute of Pharmaceutical and Medicinial Chemistry, Heinrich-Heine-University, Universitätsstrasse 1, 40225 Düsseldorf, Germany

Epigenetic control plays an important role in gene regulation through chemical modifications of DNA and post-translational modifications of histones.[1] An essential post-translational modification is the histone acetylation/deacetylation-process which is regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). The mammalian zinc-dependent HDACs family is subdivided into three classes: class I (HDACs 1-3, 8), class II (IIa: HDACs 4, 5, 7, 9; IIb: HDACs 6, 10) and class IV (HDAC 11). [2]
Recent studies have shown that class IIa enzymes are associated with neurodegenerative diseases and cancer.[3][4][5][6] Only few class IIa inhibitors have been identified due to the conserved structure of zinc-dependent HDACs. In published crystal structures of class IIa HDACs the so-called lower pocket was identified as a distinctive structural feature. [7][8]
Our aim is to design and synthesize selective HDAC class IIa inhibitors by addressing the lower pocket and by using selectivity directing zinc-binding groups like the trifluoromethyloxadiazole (TFMO) moiety.

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Disrupting HSP90 Dimerization

David Bickel[1], Thomas Kurz[1], Holger Gohlke[1,2]
[1]Institute for Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Germany; [2]John von Neumann Institute for Computing, Jülich Supercomputing Centre, Institute for Complex Systems-Structural Biochemistry (ICS-6), Forschungszentrum Jülich GmbH, Jülich, Germany

Protein-protein interactions are at the core of signal transduction within the cell and thus involved in the regulation of a wide variety of physiological and pathophysiological processes. However, only a small proportion of drugs target these interactions so far. Thus, there is an increasing interest in drug discovery to modulate protein-protein interactions. Protein-protein interfaces are considered challenging targets though, since they are comprised of wide-spread and shallow areas on the protein surface and do not show pronounced binding pockets.[1] The heat shock protein of 90 kDa (HSP90) is a molecular chaperone that is involved in tumor progression in several cancer cell lines, i.e. in chronic myelogenous leukemia. Targeting the dimerization interface in the C-terminal domain should provide a novel way to interfere with HSP90 function.[2]
By performing a structural decomposition of the effective free energy of binding of the dimerization interface, we identified clustered hotspot regions small enough to be targeted by rationally designed small molecule drugs.[3] In order to address these hotspots a class of ligand molecules was designed, which can mimic the sidechain orientation of an α-helix. In order to elucidate the binding mode of these compounds, unbiased molecular dynamics (MD) simulations were performed. The binding mode derived from these experiments will further be used to improve the activity and selectivity of these inhibitors.
The compounds synthesized so far were shown to interact with the target protein in *in vitro* assays and also exhibited activity against various leukemia cell lines. This highlights the possibility to design drug-like protein-protein interaction modulators using the structural information from the protein-protein interface.

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Modulation of sphingosine-1-phosphate sphingolipid signaling

Hjördis Brückmann[a], Aleksandra Zivkovic[a], Annika Frank[a], Faik Imeri[b], Stephanie Schwalm[c], Ruth Lyck[d], Britta Engelhardt[d], Josef Pfeilschifter[b], Andrea Huwiler[b], Holger Stark[a]
[a]Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitaetsstrasse 1, D-40225 Duesseldorf, Germany (e-mail: stark@hhu.de); [b]Institute of Pharmacology, University of Bern, Inselspital INO-F, CH-3010 Bern, Switzerland; [c]Pharmazentrum Frankfurt/ZAFES, University Hospital, Goethe University Frankfurt am Main, Germany; [d]Theodor-Kocher Institute, University of Bern, Freiestrasse 1, CH-3012 Bern, Switzerland

Sphingolipid metabolism is due to its key role in cell fate control involved in several diseases. In this pathway the main signaling molecules are sphingosine and sphingosine-1-phosphate (S1P), which exhibits its effects via five G-Protein coupled receptors (GPCRs). S1P promotes cell growth and inhibits apoptosis whereas sphingosine induces apoptosis and thereby inhibit cell growth. These impacts make the biosynthesis and GPCRs of S1P interesting target structures in cancer, inflammatory diseases and autoimmune disorders.[1]
The sphingosine kinase (SK) which is expressed in two isoforms mainly controls the balance of sphingosine and S1P. Sphingosine kinase inhibitors with dual or selective inhibitory functions can be pharmacological tools and drug candidates. They can provide insights about the different functions, interaction partners and effect on various diseases of both isoforms.[2] Starting from SKI-II [3] as a lead structure different compounds with 2-aminothiazole core have been synthesized to evaluate the influence of different lipophilic regions on the activity towards SK1 and SK2.[4]
Different targets to influence S1P signaling are its receptors which can be modulated by the nature-derived drug fingolimode, in use for Multiple sclerosis. Fingolimode is phosphorylated by SK2 to its active form and additionally inhibits SK1. Modulation of S1P receptors by fingolimode result in internalization of active receptors and reduced signaling.[5] Novel butterfly (oxazolo-oxazole) derivatives of fingolimode acted *in vitro* and *in vivo* similar to the lead structure and are promising drug candidates for cancer and autoimmune disorders.[6]

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Genome mining for the discovery of angucyclines and angucyclinones from marine *Streptomyces* and crystal structure of ColA1a in Collismycin biosynthesis

Tan Liu, Guiyang Wang, Jing Jin, Xiaoyan Yang, Xueyang Ma, Zhongyi Zhang, Yuanjie Ge, Hua Xiao, Tongtong Geng, Xiaoxu Sun, Donghui Yang, **Ming Ma** *
State key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, 38 Xueyuan Road, Haidian District, Beijing, China, 100191

Angucyclines and angucyclinones are aromatic polyketides that feature a tetracyclic benz[a]anthracene skeleton and produced by type II polyketide synthases (PKS). We reported here the PCR-guided discovery of unusual angucyclines and angucyclinones from our marine actinomycetes collections, using degenerated primers designed from the conserved amino acid sequences of KSα and KSβ. The PCR-guided strain prioritization, in combination with fermentation optimization and chemical investigation, afforded new fluostatins featuring a 6-5-6-6 ring skeleton, angucyclinones featuring new heterocycle formation, and new angucyclines featuring sugar moieties attached at C-1 position. These results highlight the structural diversity of aromatic polyketides from marine Streptomyces.
We also report the 1.8 Å crystal structure of ColA1a, one type II peptidyl carrier protein (PCP) in the starter module of nonribosomal peptide synthetase (NRPS) in collismycin biosynthesis. The structure of ColA1a possesses the typical α helix-rich fold, however, there are two additional small α helices in the loop between helix I and II, and the helix III is replaced by a one turn-containing loop, exemplifying ColA1a's special structural features. The general fold of ColA1a possesses an A/H-state, consistent with the first crystal structure of type II PCP, the BlmI in bleomycin biosynthesis. [1] These results support that the A- or H-state of PCP is artifact due to the excision from its native context.

Keywords: Angucyclines and angucyclinones; ColA1a; Collismycin; Crystal structure; Genome mining

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Identification and characterisation of the TBK1-FIP200 interaction

David Schlütermann, Jana Deitersen, Niklas Berleth, Wenxian Wu, Fabian Stuhldreier, Philip Böhler, Nora Wallot-Hieke, Maria José Mendiburo, Christoph Peter, Björn Stork
Institute of Molecular Medicine I, Medical Faculty, Heinrich Heine University Düsseldorf, Germany

Autophagy, an intracellular recycling process for damaged or long-lived proteins and organelles, is connected to several diseases like cancer, neurodegenerative and infectious disorders. The ULK1 complex, consisting of ULK1, FIP200, ATG13 and ATG101, is the main complex for initiating autophagy. FIP200 is also known to have several interaction partners with different functions apart from autophagy like cell adhesion, stress response, cell proliferation or cell growth. Using mass spectrometric analysis, we searched for unknown interaction partners and thereby identified TBK1, a key regulator in the innate immune response, as an interaction partner of FIP200. TBK1 is already connected to the process of autophagy by phosphorylating NDP52 and p62, two autophagic adaptor proteins responsible for cargo recognition. Additionally, we showed the importance of the C-terminal domain of TBK1 for the TBK1-FIP200 interaction. However, FIP200 seems to be able to negatively regulates TBK1, since the loss of FIP200 leads to an accumulation of TBK1 followed by a highly increased activation and even LPS stimulation was not able to further increase the TBK1 activation. Supportively, amino acid starvation decreases TBK1 activation. Since misregulation of TBK1 activity can promote inflammatory disorders or cancer development the interaction of FIP200 and TBK1 can be a potential therapy target.

Chemosensitizing properties of alkoxyamide-based histone deacetylase inhibitors in combination with cisplatin in head and neck cancer cell lines Cal27 and Cal27CisR

Christian Schrenk, Alexandra Hamacher, Leandro A. Alves-Avelar, Thomas Kurz, Matthias U. Kassack

Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitaetsstrasse 1, D-40225 Duesseldorf, Germany

Histone deacetylase inhibitors (HDACis) display potent anti-cancer effects in numerous cancer cells. However clinical studies show that monotherapy with HDACis have only a limited efficacy in solid tumors compared to hematological tumors. Combinations of HDACis with other anti-cancer drugs like cisplatin have been shown to be synergistic by our group. In this study, new alkoxyamide-based HDACis have been investigated for their chemosensitizing properties in the human head and neck cancer cell line Cal27 and its cisplatin-resistant clone Cal27CisR. Four compounds displayed IC_{50} values in the sub-μM to low μM range in the cellular HDACi assay. Three compounds showed sub-μM IC_{50} values in the MTT assay. The four most potent compounds revealed chemosensitizing properties in combination with cisplatin in Cal27 as well as Cal27CisR. 48 h Preincubation with 0.5 μM of the most promising compound LAK67 enhanced the sensitivity of Cal27CisR towards cisplatin by over 20-fold. The corresponding IC_{50} for this combination was lower than the IC_{50} value of cisplatin in the parental cell line Cal27, thus completely reversing cisplatin resistance of Cal27CisR. Moreover, 24h preincubation of the four most potent compounds led to synergistic enhancement of caspase 3/7 activation when combined with cisplatin. Due to their cytotoxic and HDAC inhibitory potential, these new alkoxyamide-based compounds provide promising chemical structures for further evaluation with DNA damaging compounds like cisplatin.

Enrichment of antagonists against *Escherichia coli* and other Gram-negative bacteria from environmental samples

Tino Seidemann und Rainer Kalscheuer
Institute of Pharmaceutical Biology and Biotechnology, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany

Pathogenic Gram-negative bacteria are a major health threat. This type of bacteria is far more difficult to target by antibiotics than Gram-positive species due to high intrinsic resistance based on presence of an additional outer membrane. Furthermore, they are prone to develop drug resistance through various mechanisms. The WHO declared *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacteriaceae* the microorganisms with the highest priority in research and development of new drugs. Antimicrobial resistances in general, increase the numbers of deaths and costs, while decreasing the number of treatment options.
In their natural environment, microorganisms are in a constant distress to defend themselves against other microbial species. Therefore, they are dependent on gaining a fitness advantage by developing new survival strategies such as the production of antagonistic secondary metabolites to defend their competitors. However, microorganisms producing anti-Gram-negative compounds are typically present in environmental samples only at low numbers and are masked by a huge abundance of other species, significantly hampering their isolation. In this project, a method is developed to stimulate antibacterial secondary metabolite production of environmental microorganism. By inoculation of samples with *Escherichia coli*, an artificial selection pressure is posed to enrich for antagonists against Gram-negative bacteria, facilitating their isolation and identification. As proof of concept, two *Paenibacillus* sp. have been isolated by this approach and are currently being characterized regarding their anti-Gram-negative activity.

Azaphilone derivatives from the fungus *Coniella fragariae* inhibit NF-κB activation and reduce tumor cell migration

Haiqian Yu,[1] Julia Sperlich,[2] Attila Mándi,[3] Tibor Kurtán,[3] Fabian Stuhldreier,[4] Sebastian Wesselborg,[4] Chenyin Wang,[5] Matthias Kassack,[5] Haofu Dai,[6] Nicole Teusch,[2] Zhen Liu,[*,1] Peter Proksch[*,1]

[1]Institute of Pharmaceutical Biology and Biotechnology, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany

[2] Bio-Pharmaceutical Chemistry and Molecular Pharmacology, Faculty of Applied Natural Sciences, Technische Hochschule Köln, Chempark, 51368 Leverkusen, Germany

[3] Department of Organic Chemistry, University of Debrecen, P.O. Box 400, H-4002 Debrecen, Hungary

[4] Institute of Molecular Medicine, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany

[5] Institute for Pharmaceutical and Medicinal Chemistry, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany

[6] Key Laboratory of Biology and Genetic Resources of Tropical Crops, Ministry of Agriculture, Institute of Tropical Bioscience and Biotechnology, Chinese Academy of Tropical Agricultural Sciences, Haikou 571101, China

The fungus *Coniella fragariae* was isolated from goose dung collected close to the German North Sea coast. When fermented on solid rice medium, the fungus yielded several different compounds including eleven new azaphilones (coniellins A-K) with the major compound coniellin A, one new benzofuran (5-(hydroxymethyl)-2-(1,2-dihydroxyisopropyl)-2,3-dihydrobenzofuran), as well as four known compounds (integracin C, pyrenophorol, pyrenophorin, 5-(1''-acetyloxymethylene)-2-(1,2-dihydroxyisopropyl)-2,3-dihydrobenzo-furan). All compounds were structurally elucidated by 1D and 2D NMR as well as by HR-MS. The absolute configuration of the major compound coniellin A was determined as (7R,8S,12S) by ECD calculation. Mosher's method was applied to determine the absolute configuration of coniellin E.

The major compound coniellin A showed pronounced antitumor activity against Jurkat J16 cells line and Ramos cell line with IC_{50} values 7.3 µM and 1.8 µM respectively. Mechanistic studies indicated that cytotoxicity in the low micromolar range was through inducing apoptotic cell death. Coniellin A also inhibits the transcription factor NF-κB in the triple negative breast cancer cell line MDA-MB-231 with an IC_{50} value of 4.4 µM. In a scratch wound density test, coniellin A significantly inhibited cancer cell proliferation at sublethal doses which is probably linked to the inhibition of NF-κB.

Social program

Welcome Banquet

On September 17th 2018 we will meet for a Welcome Banquet at MasterInn restaurant at 18:00 pm.

Lab viewing

During the Lab viewing on September 19th participants will have the opportunity to visit the State Key Laboratory of Natural and Biomimetic Drugs (North-West of Campus) and/or the Chemical Biology Center (same Building as the meeting room).

Sino-German Student Meeting

The participating doctoral students will have the opportunity to meet and get together in a Sino-German Student Meeting on September 18th from 16:30 -17:30 pm.

Farewell Dinner

On September 21st 2018 we will meet for a Farewell Dinner at MasterInn restaurant at 18:00 pm.

Visit of the Summer Palace in Beijing - 20th September 2018

The Summer Palace, northwest of Beijing, is considered the best preserved imperial garden in the world, and the largest of its kind still existing in China.

The Summer Palace in Beijing – first built in 1750, largely destroyed in the war of 1860 and restored on its original foundations in 1886 – is a masterpiece of Chinese landscape garden design. The natural landscape of hills and open water is combined with artificial features such as pavilions, halls, palaces, temples and bridges to form a harmonious ensemble of outstanding aesthetic value.[1]

Since 1998, the Summer Palace is inscribed as UNESCO World Heritage Site.[1]

We will visit the Summer Palace in afternoon of September 20th.

Visit of the Great Wall in Beijing - 21th September 2018

The Great Wall was continuously built from the 3rd century BC to the 17th century AD on the northern border of the country as the great military defense project of successive Chinese dynasties, with a total length of more than 20,000 kilometers. The Great Wall begins in the east at Shanhaiguan in Hebei province and ends at Jiayuguan in Gansu province to the west. Its main body consists of walls, horse tracks, watch towers, and shelters on the wall, and includes fortresses and passes along the Wall.[2]

The Great Wall reflects collision and exchanges between agricultural civilizations and nomadic civilizations in ancient China. It provides significant physical evidence of the far-sighted political strategic thinking and mighty military and national defense forces of ancient China, and is an outstanding example of the superb military architecture, technology and art of ancient China. It embodies unparalleled significance as the national symbol for safeguarding the security of the country and its people.[2]

Since 1987, the Great Wall is inscribed as UNESCO World Heritage Site.[2]

We will visit the Great Wall in a One-Day-Trip on September 21st.

Detailed information about the tours will be given during the Symposium.

[1] Website of World Heritage Convention: http://whc.unesco.org/en/list/880/ (state of 15.8.2918) Description is available under license CC-BY-SA IGO 3.0

[2] Website of World Heritage Convention: http://whc.unesco.org/en/list/438 (state of 15.8.2918) Description is available under license CC-BY-SA IGO 3.0

List of Participants (Alphabetical Order)

Yodita Asfaha
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
Yodita.asfaha@uni-duesseldorf.de

David Bickel
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
david.bickel@uni-duesseldorf.de

Hjördis Brückmann
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
hjoerdis.bruekmann@uni-duesseldorf.de

Karin Buchholz
Institute of Medical Microbiology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
karin.buchholz@uni-duesseldorf.de

Qi-Tong Chen
School of Pharmaceutical Science, Peking University
381706145@qq.com

Jana Deitersen
Institute of Molecular Medicine I, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
jana.deitersen@uni-duesseldorf.de

Daniel Drießen
Institute of Organic Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
daniel.driessen@uni-duesseldorf.de

Annika Frank
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
annika.frank@uni-duesseldorf.de

Prof. Dr. Holger Gohlke
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
John von Neumann Institute for Computing, Jülich Supercomputing Centre, Institute for Complex Systems-Structural Biochemistry (ICS-6), Forschungszentrum Jülich GmbH, Jülich, Germany
gohlke@uni-duesseldorf.de

Julian Greb
Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
j.greb@fz-juelich.de

Yvonne Gröner
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
yvonne.gröner@uni-duesseldorf.de

Dr. Martina Holz
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
grad2158@uni-duesseldorf.de

Prof. Dr. Rainer Kalscheuer
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
rainer.kalscheuer@uni-duesseldorf.de

Prof. Dr. Thomas Kurz
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
thomas.kurz@uni-duesseldorf.de

Xin Li
Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071
lixin871014@163.com

Prof. Dr. Wenhan Lin
State Key Laboratory of Natural and Biomimetic Drugs, , School of Pharmaceutical Sciences, Peking University
whlin@bjmu.edu.cn

Jian-Rong Liu
School of Pharmaceutical Science, Peking University
liujianrong2017@126.com

Prof. Dr. Yijia Lou
Institute of Pharmacology and Toxicology, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China
yijialou@zju.edu.cn

Prof. Dr. Ming Ma
State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University
mma@bjmu.edu.cn

Dr. Ling-Hong Meng
Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071
m8545303@163.com

Prof. Dr. Thomas J.J. Müller
Institute of Organic Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
thomasjj.mueller@uni-duesseldorf.de

Marc Pflieger
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
marc.pflieger@uni-duesseldorf.de

Prof. Dr. Jörg Pietruszka
Institute of Bioorganic Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
j.pietruzska@uni-duesseldorf.de

Nicola Porta
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
nicola.porta@uni-duesseldorf.de

Prof. Dr. Peter Proksch
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
proksch@uni-duesseldorf.de

Lisa Richter
Institute of Medical Microbiology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
lisa.richter.14@uni-duesseldorf.de

Prof. Dr. Stefanie Scheu
Institute of Medical Microbiology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
stefanie.scheu@uni-duesseldorf.de

David Schlütermann
Institute of Molecular Medicine I, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
david.schluetermann@uni-duesseldorf.de

Christian Schrenk
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
christian.schrenk@uni-duesseldorf.de

Tino Seidemann
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
tino.seidemann@uni-duesseldorf.de

Shabnam Shaneh Sazzadeh
Institute of Medical Microbiology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
Shabnam.ShanehSazzadeh@med.uni-duesseldorf.de

Dr. Xiao-Shan Shi
Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071
xiaoshan1511@163.com

Dr. Sander Smits
Institute of Biochemistry I, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
sander.smits@uni-duesseldorf.de

Prof. Dr. Holger Stark
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
stark@uni-duesseldorf.de

Prof. Dr. Björn Stork
Institute of Molecular Medicine I, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
bjoern.stork@uni-duesseldorf.de

Fabian Stuhldreier
Institute of Molecular Medicine I, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
fabian.stuhldreier@uni-duesseldorf.de

Nam Michael Tran-Cong
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
nam.tran-cong@uni-duesseldorf.de

Jana van Stuijvenberg
Institute of Toxicology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
jana.van.stuijvenberg@uni-duesseldorf.de

Prof. Dr. Bing-Gui Wang
Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences, Nanhai Road 7, Qingdao 266071
wangbg@ms.qdio.ac.cn

Prof. Dr. Chang-Yun Wang
Key Laboratory of Marine Drugs, the Ministry of Education of China, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China. & Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science and Technology, Qingdao 266071, China
changyun@ouc.edu.cn

Chao-Yi Wang
Key Laboratory of Marine Drugs of Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China. & Laboratory for Marine Drugs and Bioproducts, Qingdao National Laboratory for Marine Science and Technology, Qingdao 266071, China.
chaoyi0411@126.com

Dr. Cheng Wei
School of Pharmaceutical Sciences, Peking University
chengwei@bjmu.edu.cn

Chenyin Wang
Institute of Pharmaceutical and Medicinal Chemistry, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
chenyin.wang@uni-duesseldorf.de

Prof. Dr. Jun Wu
School of Pharmaceutical Sciences, Southern Medical University, 1838 Guangzhou Avenue North, Guangzhou 510515, PR China

Dr. Donghui Yang
School of Pharmaceutical Sciences, Peking University
ydhui@bjmu.edu.cn

Haiqian Yu
Institute of Pharmaceutical Biology and Biotechnology, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
haiqian.yu@uni-duesseldorf.de

Bochuan Yuan
State Key Laboratory of Natural and Biomimetic Drugs, Peking University
chuanby@163.com

Julia Zaschke-Kriesche
Institute of Biochemistry I, Heinrich Heine University Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany
julia.zaschke-kriesche@uni-duesseldorf.de

Prof. Dr. Kui Zhu
Beijing Advanced Innovation Center for Food Nutrition and Human Health, National Center for Veterinary Drug Safety Evaluation, College of Veterinary Medicine, China Agricultural University, Yuanmingyuan West Road No.2, Beijing, 100193, China
zhukcau@163.com

Pages for notes

GRK2158
Heinrich-Heine-Universität Düsseldorf
Institute of Pharmaceutical Biology
Universitätsstraße 1, Gebäude 26.23
40225 Düsseldorf
www.uni-duesseldorf.de
www.grk2158.hhu.de