GRK2158

Symposium

“Natural products and analogs against therapy-resistant tumours and microorganisms”

Program

01.-02.07.2020

Online Conference (WebEX Meetings)

Graduiertenkolleg 2158

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

Unravelling molecular resistance mechanisms against pharmacologically active compounds as well as the search for new bioactive compounds that can overcome either intrinsic or extrinsic resistance are core subjects of pharmaceutical research. This important topic will be investigated within the Research Training Group GRK2158 as exemplified by chemoresistant tumours 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 tumours 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 Research Training Group will further strengthen the already established research priorities of the HHU in the field of tumour and infectious disease research and will add the important aspect of pre-clinical drug discovery. A structured training program for graduate students includes the acquisition of career relevant key qualifications. This Research Training Group aims at forming a new generation of experts in the field of molecular drug discovery with a unique interdisciplinary capability for which there is a high demand in academia and in industrial research as well as in regulatory authorities.

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Deutsche Forschungsgemeinschaft

Program

July 1st, 2020

Time	Speaker	Topic
13:00	Holger Gohlke	Welcome and Introduction
1st Session (Chairs: Mariam Dubiel & Marco Kruppa)		
13:15 – 14:00	**Uli Kazmaier**	**Stereoselective peptide modifications – versatile tools for natural product and drug synthesis**
14:00 – 14:15	**Short Break**	
14:15 – 14:30	Moritz Klischan	Biaryl-based natural products as structural motif for pharmaceutically relevant compounds
14:30 – 14:45	Lena Berning	Characterization of autophagy-modulating natural products and derivatives for the elimination of therapy-resistant tumor cells
14:45 – 15:00	Laura Schmitt	The elimination of chemotherapy-resistant tumors via natural product-induced cell death
15:00 – 15:15	**Short Break**	
2nd Session (Chairs: Julian Greb & Lena Berning)		
15:15 – 15:45	**Sanil Bhatia**	**Novel therapeutic strategies for resistant childhood acute lymphoblastic leukemia**
15:45 – 16:00	Yodita Asfaha	Development of class IIa histone deacetylase inhibitors
16:00 – 16:15	**Short Break**	
16:15 – 16:30	Xiaoli Yang	Identification immune activating characteristics of natural products and HDAC inhibitors as novel treatment options for chemoresistant tumors and bacterial pathogens
16:30 – 16:45	Marlena Sekeres	Modulation of the DNA damage response (DDR) by natural compounds (NC) to widen the therapeutic window of anticancer drugs
16:45 – 17:00	**Short Break**	
17:00 – 18:00	**PI-Meeting / Meeting of Doctoral Students**	

The meeting links will be send in a separate email.

Program

July 2nd, 2020

Time	Speaker	Topic
3rd Session (Chairs: Julia & Moritz)		
09:30– 10:15	**Julia Bandow**	**Antibacterial strategies – from the discovery of new compound classes to antibiotic mechanism elucidation**
10:15 – 10:30	**Short Break**	
10:30 – 10:45	Marco Kruppa	Diversity-oriented synthesis of symmetrically and unsymmetrically substituted alocasin A derivatives against therapy resistant bacteria
10:45 – 11:00	Emmanuel Adeniyi	Characterization of the molecular mechanisms underlying antibacterial activity of bis-indole alkaloids
11:00 – 11:15	**Short Break**	
4th Session (Chairs: Laura Schmitt & Laura Mayer)		
11:15 – 11:30	David Bickel	Development of small-molecule suppressors of oncogenic protein oligomerization
11:30 – 11:45	Julia Gottstein	Bypassing Lantibiotic Resistance
11:45 – 12:00	Mariam Dubiel	From pharmacological screening systems to fluorescent chemical probes
12:00 – 13:30	**Lunch Break**	
Group Meetings		
13:30 – 14:00	**Cluster 1:** Characterization and optimization of apoptosis and autophagy modulating natural products and derivatives for the elimination of therapy resistant tumor cells	
14:00 – 14:30	**Cluster 2:** Natural compound / HDAC inhibitor mediated modulation of immune responses and cytostatic-induced stress responses for the resensibilization of therapy-resistant tumors	
14:30 – 15:00	**Cluster 3:** Characterization of the mode of action and medicinal chemical optimization of antimicrobial natural compounds (chloroflavonin, bisindoles and indolo[3,2-a]phenazines)	
15:00 – 15:30	**Cluster 4:** Nisin as a model system for overcoming lantibiotic resistance in bacterial pathogens	

The meeting links will be send in a separate email.

Abstracts of Talks

Stereoselective peptide modifications – versatile tools for natural product and drug synthesis

Uli Kazmaier, Institute of Organic Chemistry, Saarland University

Microorganisms are highly productive producers of natural products, and a wide range of their secondary metabolites became lead structures for the development of drugs. Peptides and cyclo(depsi)peptides formed by nonribosomal peptide synthetases (NRPS) are especially interesting from a pharmaceutical point of view. Many of these peptides contain not only (*S*)- and (*R*)-configured or *N*-methylated amino acids, but also rather unusual side chains. In classical peptide syntheses, these unusual amino acids are synthesized separately, and are subsequently coupled using suitable coupling reagents. No question, this protocol is suitable for the synthesis of a single target molecule (natural product or drug), but is by far less suited for the synthesis of libraries of related peptidic structures, as required for SAR studies or lead structure optimizations. In these cases, a concept allowing modifications in a very late stage of the synthesis would be much more attractive. Selective peptide modifications are a suitable tool to address this issue. The advantage of the rather simple side chain modifications results from the fact, that the stereogenic α-centre can be transmitted from the parent amino acid, but on the other hand one is limited to the possible modifications of a given functionalized side chain. A significantly higher structural variety can be generated *via* peptide-backbone modifications, where complete side chains can be introduced at glycine subunits.

Antibacterial strategies – from the discovery of new compound classes to antibiotic mechanism elucidation

Julia Bandow, Applied Microbiology, Ruhr University Bochum

The bacterial genus Streptomyces is well-known as a source of bioactive natural products. We recently characterized the secreted metabolome of S. chartreusis using high-resolution LC-MS/MS. We detected more than one thousand substances, the vast majority of which could not be identified based on publicly available MS/MS databases. Further, we found that there is limited overlap among the natural products secreted by different Streptomyces isolates. Future efforts will be directed at identifying structurally novel antibacterial agents produced by the isolates. To elucidate their antibacterial targets and mechanisms of action, we employ classical methods as well as complementary system-based approaches. The chromatographic coelution of drugs with their target proteins in native HPLC can be exploited to shortlist potential targets, as we showed in a proof-of-concept for the transcription inhibitor rifampicin. We employed this method to identify the target of the synthetic organometallic DS50 and complemented it with pull-down experiments employing a biotinylated DS50 derivative. We found that DS50 targets translation by inhibiting EF-Tu. A library of proteomic responses to sublethal doses of >90 antibacterial agents is available to study the physiological impact of antibiotics. The comparison with the library revealed that the mechanism of action of DS50 likely differs from that of known EF-Tu inhibitors.

Novel therapeutic strategies for resistant childhood acute lymphoblastic leukemia

Sanil Bhatia[1], Julian Schliehe-Diecks[1], Heinz Ahlert[1], Niklas Dienstbier[1], Melf Sönnichsen[1], Jing Yang[1], Vitalij Woloschin[3], David Bickel[2], Nina Ressing[2], Benedikt Frieg[3], Finn K. Hansen[2], Matthias Kassack[3], Ute Fischer[1], Holger Gohlke[3], Thomas Kurz[3] and Arndt Borkhardt[1]

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During recent decades, the event-free survival of childhood acute lymphoblastic leukemia (ALL) has improved up to 80%, but there are still subgroups with a dismal prognosis. Besides that, the current treatment approaches are often linked with severe side effects and still around 20% children relapse, and later succumb to the disease. This potentiates the need to develop novel therapeutic strategies, which are active against resistant leukemia subtypes and at the same time offer low toxicity in patients. We, therefore, i) perform high throughput drug screening and later integrate drug sensitivity vs. resistant profiles to the genetics and transcriptomics profiles of diagnostics/relapse leukemic samples which allow us better stratification of the existing therapies and in finding novel and overlooked biomarkers. ii) Besides that, we are actively involved in developing and characterizing novel precision compounds in collaboration with Institute of Pharmaceutical Chemistry HHU Düsseldorf, which target oncogene stabilization in resistant leukemic subtypes, e.g. by targeting CTD of HSP90 and HDACs. iii) Furthermore, to understand the development of human leukemia we generate genetically engineered mouse models (GEMM). Taken together, these approaches represent a rational effort towards the development of novel targeted strategies for the treatment of relapsed/refractory ALL with lower toxicity burden.


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