13:00 **Welcome**
Dekan Prof. Dr.-Ing. Kai-Olaf Hinrichsen
Apl. Prof. Dr. Wolfgang Eisenreich

13:15 **Hans-Fischer-Memory-Award 2017**
Laudatio by **Prof. Dr. Karsten Reuter**
Speech of the awardee **Dr. Harald Oberhofer**

13:45 **Keynote Lecture**
Prof. Dr. Michel Rohmer
Université de Strasbourg/CNRS
Biosynthesis of isoprene units in bacteria: the non-programmed and non-programmable discovery of the methylerythritol phosphate (MEP) pathway

14:30 **Coffee-break**

Topic: Malaria

15:00 **Prof. Dr. Ingrid Faye**
Stockholm University, Department of Molecular Biosciences, The Wenner-Gren Institut
A Malaria Signal for Immediate Transmission

15:30 **Prof. Dr. Matt Bogyo**
University School of Medicine, Stanford
Development of Highly Selective Inhibitors of the Malaria Proteasome

16:00 **Prof. Dr. Peter Seeberger**
Max-Planck-Institute of Colloids and Interfaces, Potsdam-Golm
Preventing and Fighting Malaria: Carbohydrate Vaccines and Flow Chemistry

16:30 **Dr. Matthias Witschel**
BASF-SE, Ludwigshafen
Leads from Crop Protection against Malaria

17:00 **Social Event (Beer and Brezels)**

18:30 **Dinner (for Invited Guests)**

Hans-Fischer-Gesellschaft e.V.
http://Hans-Fischer-Gesellschaft.de/

Technische Universität München
Department of Chemistry
Chair of Biochemistry
Prof. Dr. Michael Groll

Venue:
TUM Department of Chemistry
Hans-Fischer Auditorium
Lichtenbergstr. 4
85747 Garching

Information:
Technische Universität München
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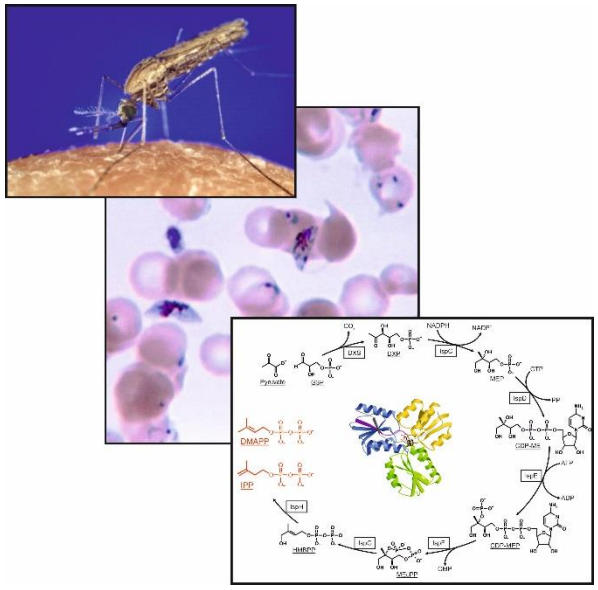
25th Hans-Fischer-Symposium

6th November 2017

Topic:

Malaria



Michel Rohmer

Biosynthesis of isoprene units in bacteria

The discovery of a major, novel metabolic pathway towards the formation of isoprene units in bacteria is in fact a side-product of our research on the chemistry and biochemistry of bacterial triterpenoids of the hopane series. The presence of a carbon/carbon bond between a triterpene moiety and a C_5 polyhydroxylated *n*-alkyl side-chain represents a unique feature in this series. Labeling experiments were therefore designed in order to determine the origin of this side-chain, which revealed to be a D-ribose derivative, shed light on unexpected labeling patterns of the isoprene units. Indeed, incorporation of ^{13}C labeled precursors (acetate or glucose isotopomers) into the bacterial hopanoids disclosed a novel biosynthetic pathway towards isoprene units, corresponding to an alternative to the classical mevalonate route first identified in liver tissues and in yeast. Complete elucidation required molecular biology techniques, including gene identification and characterization of the enzymes. Some striking aspects of discovery and elucidation of this long overlooked biosynthetic route will be discussed.

Ingrid Faye

A malaria signal for immediate transmission

Malaria infections render humans more attractive for *Anopheles gambiae* mosquitoes but the underlying molecular mechanisms is not well understood. We can mimic the effects of parasitized humans on mosquito behavior by offering a meal of normal human blood supplemented with the parasite specific isoprenoid precursor, (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP). HMBPP triggers an increased release of CO_2, aldehydes and monoterpenes in a complex mixture that strongly enhances female mosquito attraction. Females take larger blood meals of the HMBPP supplemented blood and yet mosquito fecundity and lifespan are unaffected. Moreover, when HMBPP is administered in a *Plasmodium falciparum* infected blood meal, the number of parasites developing in the mosquito is increased. Transcriptome analyses reveal temporal up-regulation of immune genes as well as neural genes potentially involved in foraging and feeding while genes involved in oogenesis and translation are down-regulated. Our work sheds light on how transmission success evolved in *Plasmodium* and how parasites in general may influence the behavior of their hosts.

Matt Bogyo

Development of highly selective inhibitors of the malaria Proteasome

I will present our recent advances using chemical probes to develop selective inhibitors of the proteasome from the parasite pathogen *Plasmodium falciparum*, the causative agent of malaria. The proteasome is a multi-component protease complex responsible for regulating key processes such as the cell cycle and antigen presentation. Proteasome inhibitors have been shown to be toxic for the parasite at all stages of its life cycle, including the transmissive gametocyte stages. However, all compounds that have been tested also inhibit the mammalian proteasome resulting in toxicity. We used a recently developed substrate profiling method to uncover differences in the specificities of the human and parasite 20S proteasome cores. We designed inhibitors based on amino acid preferences specific to the P. falciparum proteasome, and found that they preferentially inhibit the tryptic-like subunit β2. We also determined the structure of the *P. falciparum* 20S proteasome bound to our inhibitor using cryo-EM and single particle analysis, to a resolution of 3.6 Å. These data reveal the unusually open *P. falciparum* β2 active site and provide valuable information regarding active site architecture that can be used to further refine inhibitor design. Furthermore, we observed growth inhibition synergism with low doses of this β2 selective inhibitor in artemisinin (ART) sensitive and resistant parasites. Finally, we demonstrated that a parasite selective inhibitor attenuates parasite growth in vivo without significant toxicity to the host. Thus, the *Plasmodium* proteasome is a chemically tractable target for next generation anti-malarial agents.

Peter Seeberger

Preventing and Fighting Malaria: Carbohydrate Vaccines and Flow Chemistry

Most pathogens including bacteria, fungi, viruses and protozoa carry unique glycans on their surface. Currently, several vaccines against bacteria are marketed very successfully. Since many pathogens cannot be cultured and the isolation of pure oligosaccharides is extremely difficult, synthetic oligosaccharide antigens provide now a viable alternative. The automated synthesis platform, has been commercialized. The quality control of synthetic oligosaccharides by ion mobility mass spectrometry (IM-MS) is fast and extremely sensitive. Currently, the laboratory is pursuing the development of several semi- and fully synthetic carbohydrate vaccines against severe bacterial infections, including multi-resistant hospital acquired infections. In addition to their function as antigens, synthetic oligosaccharides serve as tools to create monoclonal antibodies, and to establish glycan microarrays to map vaccine epitopes. Diagnostic and preventive approaches against a host of bacteria, fungi, and parasites are being pursued.

In recent years continuous flow systems have become increasingly interesting to practitioners of synthetic chemistry. Described is the use of continuous flow systems to produce drug substances and other chemicals via multi step reactions including continuous purification. The anti-malaria drug artemisinin and its derivatives as well as other life-saving drugs are used as examples.

Matthias Witschel

Leads from Crop Protection against Malaria

Many of the tropical disease pathogens, causing e.g. malaria, sleeping sickness or Chagas disease, have very similar essential enzymatic pathways as plants, but also as fungi or even insects. Therefore, in a sabbatical with Prof. F. Diederich, ETH Zürich, we examined in how far crop protection knowhow and leads could be used to fight these diseases. Many targets and lead structures could be validated based on discontinued projects from BASF crop protection research, and several are currently followed up in cooperations with academic groups. Very interesting sets of antimalarial leads could be developed from inhibitors of the non-mevalonate pathway that had been identified in herbicidal HTS-programs. In the most advanced project, antimalarial SHMT inhibitors, that also originated from a target based herbicide program, activity in the animal model could be shown.

Based on the resulting discussions and collaborations several further novel projects, e.g. for new antimalarial bednets and potential other applications of agrochemicals, have been initiated and will be presented.