Joint meeting of the 20th Anniversary
Drug Design & Development Seminar (DDDS)
of the German Society for Parasitology (DGP)
&
the LOEWE Center DRUID

March 26th – 29th, 2019
Cover legend

Upper series (from left to right): *Toxoplasma* rosettes (kindly provided by Dominique Soldati-Favre, University of Geneva, CH); VB-201 is a Toll-like receptor-2 and CD14 targeting choline-based phospholipid that was shown to be efficacious in animal models of *Cryptosporidium* infection (Arnab Chatterjee, California Institute for Biomedical Research, US; Janes *et al.* (2018) PNAS 115, no. 42, 10750–10755); Human macrophages infected with *Leishmania donovani* (kindly provided by Julio Martin, Kinetoplastid Unit, Global Health R&D, GSK, ES).

Lower series (from left to right): Adult *Schistosoma mansoni in-vitro* (kindly provided by Conor Caffrey, University of California San Diego, US); juvenile *Fasciola hepatica* with stained stem-cell-like neoblasts (green) (kindly provided by Aaron Maule, Queen’s University Belfast, UK); *Ixodes ricinus* ticks (kindly provided by Petr Kopáček, Czech Academy of Sciences, České Budějovice, CZ).

We gratefully acknowledge the financial support of:
About the Drug Design & Development Seminar (DDDS)
The Drug Design & Development Seminar (DDDS) was founded in 1999 as an active working group of the German Society for Parasitology, by Prof. Dr. Peter Köhler (University of Zürich, CH), Prof. Dr. Rolf Walter (BNI, Hamburg, DE), and Prof. Dr. Heiner Schirmer (University of Heidelberg, DE). Since 2004, Prof. Dr. Paul M. Selzer (Boehringer Ingelheim Vetmedica GmbH, Ingelheim, DE) is the sole coordinator of the DDDS, transferring the meeting into an international well-recognized scientific forum. Exchange of scientific information about anti-parasitic chemotherapy between universities, industry, and other research organizations continues to be important to accelerate anti-parasitic drug development. The DDDS is open to all scientists and professionals interested in the field of anti-parasitic research. The DDDS aims at connecting human and veterinary health by complementary approaches in medical and veterinary parasitology and medicinal chemistry to stimulate One-Health approaches to combat parasitic diseases. The main topics include but are not limited to:

- Target identification and validation
- Identification of modulators
- Synthesis and optimization of lead compounds towards marketable drugs
- Delivery of active compounds to infected hosts

About the LOEWE Center DRUID
The LOEWE Center DRUID, funded by the Hessian initiative for scientific and economic excellence, unites experts from leading medical universities in Hesse as well as from the Paul-Ehrlich-Institute (PEI) in Langen and the University of Applied Sciences of Central Hesse. Aim of DRUID is to investigate urgent issues in identifying and characterizing potential target molecules for the development of drugs, vaccines, and diagnostic tools to combat poverty-associated, neglected infectious diseases. For details, see: www.loewe-druid.de.
Venue

Biomedizinisches Forschungszentrum Seltersberg (BFS)
Schubertstraße 81
35392 Gießen

http://www.uni-giessen.de/faculties/bfs?set_language=en

How to get there

By train:
Leave the main station (BHF), turn right, go up the (stone) stairs and follow the marked route (~ 1.6 km) until you reach the venue (BFS).
Alternatively, you can use taxi or bus (no. 10 at platform 1, in front of the main station; get out at “Hayden” street).
If you have booked Hotel Heyligenstaedt, you can also use bus no. 10. In this case, get out at “Aulweg/Wartweg” and go down the street to Aulweg 41 (right side).
Here you find more information about buses in Giessen:
https://www.swg-verkehr.de/fahrplaene/

By long-distance coach:
https://www.busliniensuche.de/busverbindungen/giessen/
https://www.goeuro.de/fernbus/

By car:
Giessen is surrounded by the highways A480 and A485. These highways are connected to the highways A5 and A45.

Here you find more information (pdf-download available):
https://de.wikipedia.org/wiki/Gie%C3%9Fener_Ring
### Program Overview

**Tuesday, 26.03.2019**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>17:00</td>
<td>Registration &amp; Poster Set-Up</td>
</tr>
<tr>
<td>18:00</td>
<td>Welcome Reception at the BFS Conference Venue</td>
</tr>
</tbody>
</table>

**Wednesday, 27.03.2019**

<table>
<thead>
<tr>
<th>Time</th>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:00</td>
<td>Martin Kramer, Dean of the Faculty Veterinary Medicine, JLU Giessen</td>
<td>Welcome and Introduction</td>
<td></td>
</tr>
<tr>
<td>09:00</td>
<td>Christoph G. Grevelding, Institute of Parasitology, JLU Giessen</td>
<td>Welcome and Introduction</td>
<td></td>
</tr>
<tr>
<td>09:00</td>
<td>Katja Becker, Institute of Biochemistry &amp; Molecular Biology, JLU Giessen</td>
<td>Welcome and Introduction</td>
<td></td>
</tr>
<tr>
<td>09:00</td>
<td>Paul M. Selzer, Boehringer Ingelheim Vetmedica GmbH</td>
<td>Welcome and Introduction</td>
<td></td>
</tr>
<tr>
<td>09:00</td>
<td>Sandra Noack, Boehringer Ingelheim Vetmedica GmbH</td>
<td>Welcome and Introduction</td>
<td></td>
</tr>
<tr>
<td>09:20</td>
<td>Dominique Soldati-Favre</td>
<td>Dissection of the fundamental roles played by apicomplexan aspartyl proteases in establishment of parasitism</td>
<td>University of Geneva, CH</td>
</tr>
<tr>
<td>09:20</td>
<td>Miray Tonk</td>
<td>The <em>Drosophila melanogaster</em> antimicrobial peptides Mtk-1 and Mtk-2 are active against the malarial parasite <em>Plasmodium falciparum</em></td>
<td>Justus Liebig University Giessen, DE</td>
</tr>
<tr>
<td>09:20</td>
<td>Thomas Jacobs</td>
<td>CD4* T-cell response and regulation in acute and chronic malaria</td>
<td>Bernhard Nocht Institute Hamburg, DE</td>
</tr>
<tr>
<td>09:40</td>
<td>Isabell Berneburg</td>
<td>Glucose 6-phosphate dehydrogenases of different pathogens as potential drug targets</td>
<td>Justus Liebig University Giessen, DE</td>
</tr>
<tr>
<td>09:40</td>
<td>Daniel Sojka</td>
<td><em>Babesia</em> proteasome as a drug target</td>
<td>Czech Academy of Sciences, CZ</td>
</tr>
<tr>
<td>09:40</td>
<td>Annette Kaiser</td>
<td>Druggable targets in cyclic nucleotide signaling pathways in apicomplexan parasites and kinetoplastids against disabling protozoan diseases in humans</td>
<td>University Duisburg-Essen, DE</td>
</tr>
<tr>
<td>09:40</td>
<td>Rosa Isela Grote-Gálvez</td>
<td>Tim-3 blockade decreases parasitic load in acute <em>Trypanosoma cruzi</em> infection</td>
<td>Bernhard Nocht Institute Hamburg, DE</td>
</tr>
<tr>
<td>12:00</td>
<td>Lunch break</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Program Overview

<table>
<thead>
<tr>
<th>Wednesday, 27.03.2019</th>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:10-14:50</td>
<td>Keynote</td>
<td>Julio Martin</td>
<td>Unfolding drug discovery for infectious diseases of the developing world through open innovation</td>
</tr>
<tr>
<td>14:50-15:10</td>
<td>Session Chair: Paul M. Selzer Boehringer Ingelheim Vetmedica GmbH</td>
<td>Maria Paola Costi</td>
<td>Fragment-based drug discovery approach for the identification of new inhibitors of <em>Trypanosoma brucei</em> PTR1</td>
</tr>
<tr>
<td>15:10-15:30</td>
<td></td>
<td>Geert Jan Sterk</td>
<td>Structure-based drug discovery for African sleeping sickness by targeting a subpocket in <em>Trypanosoma brucei</em> phosphodiesterase B1</td>
</tr>
<tr>
<td>15:30-15:50</td>
<td></td>
<td>Amelie Kraus</td>
<td>How does chromatin regulate RNAPII transcription in <em>Trypanosoma brucei</em>?</td>
</tr>
<tr>
<td>15:50-16:30</td>
<td><strong>Coffee break</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:30-16:50</td>
<td></td>
<td>Christian J. Janzen</td>
<td>How does the histone methyltransferase DOT1B influence antigenic variation and developmental differentiation of <em>Trypanosoma brucei</em>?</td>
</tr>
<tr>
<td>16:50-17:10</td>
<td>Session Chair: Anja Taubert JLU Giessen</td>
<td>Laura S. M. Müller</td>
<td>Genome organization and DNA accessibility control antigenic variation in trypanosomes</td>
</tr>
<tr>
<td>17:10-17:30</td>
<td></td>
<td>Joachim Müller</td>
<td>Resistance formation to nitro drugs in <em>Giardia lamblia</em>: Comparative proteomics of three resistant strains and their respective wild-types</td>
</tr>
<tr>
<td>17:30-17:50</td>
<td></td>
<td>Panagiotis Karanis</td>
<td>The necessity for the development of an axenic <em>in vitro</em> mass cultivation system for <em>Cryptosporidium</em></td>
</tr>
<tr>
<td>18:00-19:30</td>
<td><strong>Poster session &amp; evaluation with snacks and drinks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Name</td>
<td>Title</td>
<td>Institution</td>
</tr>
<tr>
<td>--------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>09:00</td>
<td>Keynote</td>
<td>Conor Caffrey</td>
<td>University of California San Diego</td>
</tr>
<tr>
<td>09:40</td>
<td>Session Chair:</td>
<td>Jan Dvorak</td>
<td>Czech University of Life Sciences, Prague, CZ</td>
</tr>
<tr>
<td>09:40</td>
<td></td>
<td>Mammalian glutamate carboxypeptidase orthologs in helminths: functions of potential drug targets</td>
<td>Czech University of Life Sciences, Prague, CZ</td>
</tr>
<tr>
<td>10:00</td>
<td></td>
<td>Martin Horn</td>
<td>Czech Academy of Sciences, Prague, CZ</td>
</tr>
<tr>
<td>10:00</td>
<td></td>
<td>Identification and evaluation of peptidases of the blood fluke Schistosoma mansoni as drug targets</td>
<td>Czech Academy of Sciences, Prague, CZ</td>
</tr>
<tr>
<td>10:20</td>
<td></td>
<td>Coffee break</td>
<td></td>
</tr>
<tr>
<td>11:00</td>
<td></td>
<td>Alejandra M. Peter Ventura</td>
<td>Philipps University Marburg, DE</td>
</tr>
<tr>
<td>11:00</td>
<td></td>
<td>Biarylalkylocarboxylic acid derivatives as potential antischistosomal agents</td>
<td>Philipps University Marburg, DE</td>
</tr>
<tr>
<td>11:20</td>
<td>Session Chair:</td>
<td>Franco Falcone</td>
<td>University of Nottingham, UK</td>
</tr>
<tr>
<td>11:20</td>
<td></td>
<td>Schistosoma mansoni Mitogen Activated Protein Kinases: Validation as potential targets and screening of the Nottingham Managed Chemical Compound collection for inhibitors using a novel universal kinase binding assay</td>
<td>University of Nottingham, UK</td>
</tr>
<tr>
<td>11:40</td>
<td></td>
<td>Georg A. Rennar</td>
<td>Philipps University Marburg, DE</td>
</tr>
<tr>
<td>11:40</td>
<td></td>
<td>Dithiocarbamates as potential agents against schistosomiasis</td>
<td>Philipps University Marburg, DE</td>
</tr>
<tr>
<td>12:00</td>
<td></td>
<td>Helmut Haas</td>
<td>helminGuard, Sülfeld/Borstel, DE</td>
</tr>
<tr>
<td>12:00</td>
<td></td>
<td>Drug screening on live schistosomes for anti-parasitic compound discovery</td>
<td>helminGuard, Sülfeld/Borstel, DE</td>
</tr>
<tr>
<td>12:20</td>
<td></td>
<td>Lunch break</td>
<td></td>
</tr>
<tr>
<td>13:50</td>
<td>Keynote</td>
<td>Arnab Chatterjee</td>
<td>California Institute for Biomedical Research, US</td>
</tr>
<tr>
<td>14:30</td>
<td></td>
<td>ReFRAME: A comprehensive drug repurposing library and its application to the treatment of cryptosporidiosis</td>
<td>California Institute for Biomedical Research, US</td>
</tr>
<tr>
<td>14:30</td>
<td>Session Chair:</td>
<td>Nermina Vejzagić</td>
<td>TU Munich, DE</td>
</tr>
<tr>
<td>14:30</td>
<td></td>
<td>A novel cell-free method to culture Schistosoma mansoni from cercariae to juvenile worm stages for in vitro drug testing</td>
<td>TU Munich, DE</td>
</tr>
<tr>
<td>14:50</td>
<td></td>
<td>Martina Sombetzki</td>
<td>University Medical Center, Rostock, DE</td>
</tr>
<tr>
<td>14:50</td>
<td></td>
<td>When non-specific beats specific treatment: Behind the scene of T-cell mediated hepatic fibrosis in Schistosoma mansoni infection.</td>
<td>University Medical Center, Rostock, DE</td>
</tr>
<tr>
<td>15:10</td>
<td></td>
<td>Oliver Weth</td>
<td>Justus Liebig University Giessen, DE</td>
</tr>
<tr>
<td>15:10</td>
<td></td>
<td>Deorphanizing G protein-coupled receptors in Schistosoma mansoni by yeast two-hybrid analyses</td>
<td>Justus Liebig University Giessen, DE</td>
</tr>
<tr>
<td>15:30</td>
<td></td>
<td>Coffee break</td>
<td></td>
</tr>
</tbody>
</table>

Program Overview
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Chair</th>
<th>Name</th>
<th>Title</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>16:10</td>
<td>Keynote</td>
<td>Aaron Maule</td>
<td>Juvenile liver fluke stem cells, growth dynamics and therapeutics</td>
<td>Queen's University Belfast, UK</td>
<td></td>
</tr>
<tr>
<td>16:50</td>
<td>Session</td>
<td>Simone Häberlein</td>
<td>Aldehyde dehydrogenases as potential drug targets in the liver fluke <em>Fasciola hepatica</em></td>
<td>Justus Liebig University Giessen, DE</td>
<td></td>
</tr>
<tr>
<td>17:10</td>
<td>Chair</td>
<td>Klaus Brehm</td>
<td><em>Echinococcus</em> stem cells and the development of novel drugs against alveolar echinococcosis</td>
<td>University Würzburg, DE</td>
<td></td>
</tr>
<tr>
<td>17:30</td>
<td></td>
<td>Britta Lundström-Stadelmann</td>
<td>Identification of novel drug targets in <em>Echinococcus multilocularis</em> by metabolomics</td>
<td>University of Bern, CH</td>
<td></td>
</tr>
<tr>
<td>17:50</td>
<td></td>
<td>Reto Rufener</td>
<td>Screening of the MMV Pathogen Box reveals the cytochrome $bc_1$ complex as a drug target in <em>E. multilocularis</em></td>
<td>University of Bern, CH</td>
<td></td>
</tr>
<tr>
<td>18:30</td>
<td>Bus transfer (return) to dinner location / conference dinner</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>09:30</td>
<td>Keynote</td>
<td>Petr Kopáček</td>
<td>Vulnerable molecular targets in tick physiology</td>
<td>Czech Academy of Sciences, České Budějovice, CZ</td>
<td></td>
</tr>
<tr>
<td>10:10</td>
<td>Session</td>
<td>Jan Perner</td>
<td>Haem biology in metazoan parasites</td>
<td>Czech Academy of Sciences, České Budějovice, CZ</td>
<td></td>
</tr>
<tr>
<td>10:30</td>
<td>Chair: Jan Dvorak</td>
<td>José Maria Alunda</td>
<td>Predictive models in anti-parasite drug discovery: from bench (through animal cage) to bedside</td>
<td>Complutense University of Madrid, ES</td>
<td></td>
</tr>
<tr>
<td>10:50</td>
<td>Coffee break</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11:20</td>
<td>Session</td>
<td>Carsten A. Vock</td>
<td>On the development of metal-based drugs as antiparasitic agents</td>
<td>University of Vienna, AT</td>
<td></td>
</tr>
<tr>
<td>11:40</td>
<td>Chair: Joachim Geyer</td>
<td>Arnold Grünweller</td>
<td>The DEAD-Box RNA helicase eif4A as a novel broad-spectrum antiviral target</td>
<td>Philipps University Marburg, DE</td>
<td></td>
</tr>
<tr>
<td>12:00</td>
<td></td>
<td>Christin Müller</td>
<td>Illuminating the involvement of lipids in coronavirus replication</td>
<td>Justus Liebig University Giessen, DE</td>
<td></td>
</tr>
<tr>
<td>12:20</td>
<td>Wrap-up and Goodbye</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12:40</td>
<td>Final Lunch</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poster</td>
<td>Name</td>
<td>Title</td>
<td>Institution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td>Yang Zheng</td>
<td>Optimization of a phenotypic hit, NPD-2975, for the African sleeping sickness</td>
<td>University Amsterdam, NL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>Luise Robbertse</td>
<td>Towards specific treatment of babesiosis based on selective proteasome inhibition</td>
<td>Czech Academy of Sciences, CZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>Melanie Moser</td>
<td>Generation of transgenic <em>P. falciparum</em> lines for functional characterization of genes putatively involved in sexual differentiation</td>
<td>Justus Liebig University Giessen, DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>Adela Jilkova</td>
<td>Exploring druggable hot spots in <em>S. mansoni</em> cathepsin B1 for structure-based design of vinyl sulfone inhibitors</td>
<td>Czech Academy of Sciences, CZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>Yves-Nathan T. Tian-Bi</td>
<td>Schistosomes and snails in Côte d'Ivoire: hybrid schistosome infections and control</td>
<td>UFR Biosciences, CIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P6</td>
<td>Mandy Beutler</td>
<td>Characterisation of potential target molecules in <em>Schistosoma mansoni</em></td>
<td>Justus Liebig University Giessen, DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P7</td>
<td>Tom L. Gallinger</td>
<td>Dithiocarbazate derivatives as potential anthelmintic agents against <em>Schistosoma mansoni</em></td>
<td>Philipps University Marburg, DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P8</td>
<td>Anne Rabes</td>
<td>CTLA4-Ig – a potential drug for the treatment of hepatic fibrosis in schistosomiasis?</td>
<td>University Medical Center Rostock, DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P9</td>
<td>Franziska Winkelmann</td>
<td>Human serum differentially impacts membrane turnover of male and female <em>Schistosoma mansoni</em></td>
<td>University Medical Center Rostock, DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P10</td>
<td>Simone Häberlein</td>
<td>Insects in anthelmintics discovery: lady beetle-derived harmine as novel anti-parasitic “swiss army-knife”?</td>
<td>Justus Liebig University Giessen, DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P11</td>
<td>Hisham Houhou</td>
<td>Abl kinases as potential targets for candidate compounds in the liver fluke <em>Fasciola hepatica</em></td>
<td>Justus Liebig University Giessen, DE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P12</td>
<td>Angelika Sturm</td>
<td><em>P. falciparum</em> pre-erythrocytic screening platform: screening for causal prophylactics</td>
<td>TropIQ Health Sciences NL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dissection of the fundamental roles played by apicomplexan aspartyl proteases in establishment of parasitism

Gaëlle Lentini, Rouaa Ben Chaabene, Budhaditya Mukherjee and Dominique Soldati-Favre

Department of Microbiology and Molecular Medicine, Faculty of Medicine - University of Geneva, CMU, 1 rue Michel-Servet 1211 Geneva 4 Switzerland
E-mail: dominique.soldati-favre@unige.ch

The phylum of Apicomplexa groups life-threatening pathogens for humans and animals. Central to the survival and dissemination of these obligate intracellular parasites is their capacity to actively invade and egress from host cells. An arsenal of secretory proteins are sequentially discharged from specialized secretory organelles during egress and invasion which act as perforins, adhesins, proteases, or kinases. Host attachment triggers the discharge of rhoptry proteins, RONs and ROPs that participate in the entry by forming the moving junction and in subversion of host cellular functions, respectively. We previously showed that the Toxoplasma gondii aspartyl protease 3 (TgASP3) serves as essential maturase for microneme and rhoptry proteins and thus plays a crucial role in invasion and egress [1]. The orthologs of TgASP3 in the malaria parasites, Plasmepsin IX and X, fulfill equally fundamental functions in all the invasive stages of malaria parasites [2]. Remarkably, parasites depleted in TgASP3 failed to discharge their rhoptries by an unknown mechanism. A global terminal amine isotopic labeling of substrates (TAILS) analysis identified TgTAILS8 as a novel TgASP3 substrate implicated in rhoptry discharge. TgTAILS8 is a type II transmembrane RON kinase. ASP3 cleavage site on TAILS8 has been mapped and its relevance for the kinase function is under investigation. T. gondii possesses a large family of secreted ROP kinases impacting on virulence and pathogenesis. Among them TAILS8 is the first active RON kinase implicated in organelle discharge and invasion.

[1] Dogga et al., 2017. eLife e27480
GSK is committed to global health and to discover innovative medicines that combat diseases of the developing world (DDW). No commercial return, but access to medicine is sought, and we pledge work hand-in-hand with public and private partners. The Open Innovation lays on three pillars: Open Lab (providing access to our know-how and infrastructure), Open Source (sharing our data and assets with the worldwide research community) and Patent Pool (flexible IP protection).

We will describe how we are leveraging Open Innovation to build a portfolio of assets as well as unveiling new targets, mechanisms of action and chemical biology knowledge. In this paper we will focus on two major kinetoplastid NTDs, i.e. visceral leishmaniasis (VL) and Chagas disease (CD). The GSK 1.8 million compounds collection has been screened phenotypically against their causative parasites, i.e. respectively *Leishmania donovani* and *Trypanosoma cruzi*, as well as *T. brucei* [1]. As a result, three anti-kinetoplastid boxes of 200 compounds each have been assembled representing the chemical and biological diversity identified. We envisage that the collaborative network which is emerging thanks to researchers and institutions will contribute to the research community with new therapeutic targets, chemical tools and further lead discovery programs.

Furthermore, we will also review some of the most advanced NCEs discovered for VL, which have revealed novel targets unprecedented in the clinic [2].

Abstract of Keynote Talks

Drug discovery for schistosomiasis at the University of California San Diego

Conor R. Caffrey1, Steven Chen2, Brian M. Suzuki1, Michelle R. Arkin2, R. Jeffrey Neitz2, Rahul Singh3, Alan R. Wolfe4, Leslie Z. Benet4, David L. Nelson5

The CDIPD at UC San Diego (http://cdipd.org/) is engaged in drug discovery for parasitic diseases of poverty. For schistosomiasis, treatment and control precariously rely on just one partially effective drug, praziquantel (PZQ). New drugs are needed. The CDIPD has designed a high-content drug-screening platform to quantify the chemically-induced static and kinetic responses of Schistosoma mansoni. I will describe the platform’s development and implementation via a custom-built graphical user interface. Screening data for high-value small molecule collections will be presented. Next, I will re-examine compounds known as alkylaminoalkanethiosulfates that derive from a 1960’s Cold War program in the United States to develop radiation-protection agents and then shown by Brazilian colleagues to kill S. mansoni in mice. In our own mouse infection model, one sulfate in particular was competitive with PZQ in terms of its single-dose efficacy against mature and PZQ-refractory juveniles. In vitro metabolic profiling of this lead and its disposition in mice identified a putative metabolic pathway. Chemical synthesis followed by in vitro and/or in vivo testing of two key metabolites confirmed schistosomicidal activity for one of them, including against Schistosoma haematobium. The identification of a lead and at least one cidal principle in an old chemical series may yet yield a drug that either complements or provides an alternative to PZQ.

1Center for Discovery and Innovation in Parasitic Diseases, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, USA; 2Small Molecule Discovery Center, Department of Pharmaceutical Chemistry, University of California San Francisco, USA; 3Department of Computer Science, San Francisco State University, San Francisco, USA; 4Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, USA; 5Federal University of the Valleys of Jequitinhonha and Mucuri, Brazil.

E-mail: ccaffrey@ucsd.edu
ReFRAME: A comprehensive drug repurposing library and its application to the treatment of cryptosporidiosis

Jeff Janes¹, Megan E. Young¹, Emily Chen¹, Nicole H. Rogers¹, Sebastian Burgstaller-Muehlbacher², Laura D. Hughes², Melissa S. Love¹, Mitchell V. Hull¹, Kelli L. Kuhen¹, Ashley K. Woods¹, Sean B. Joseph¹, H. Michael Petrassi¹, Case W. McNamara¹, Matthew S. Tremblay¹, Andrew I. Su², Peter G. Schultz¹, Arnab K. Chatterjee¹

¹Calibr at Scripps, La Jolla, CA 92037. United States; ²Department of Integrative, Structural and Computational Biology at Scripps Research, La Jolla, CA 92037 United States
E-mail: achatterjee@scripps.edu

The chemical diversity and known safety profiles of drugs previously tested in humans makes them a valuable set of compounds to explore potential therapeutic utility in indications outside those originally targeted, especially neglected tropical diseases. This practice of "drug repurposing" has become commonplace in academic and other non-profit drug discovery efforts, with the appeal that significantly less time and resources are required to advance a candidate into the clinic. Here we report a comprehensive open-access, drug repositioning screening set of 12,000 compounds (termed ReFRAME) that was assembled by combining three widely-used commercial drug competitive intelligence databases (Clarivate Integrity, GVK Excelra GoStar and Citeline Pharmaprojects), together with extensive patent mining of small molecules that have been dosed in humans. To date ~12,000 compounds (~80% of compounds identified from data mining) have been purchased or synthesized, and subsequently plated for screening. To exemplify its utility, this collection was screened against Cryptosporidium spp., a major cause of childhood diarrhea in the developing world, and two active compounds previously tested in humans for other therapeutic indications were identified. Both compounds, VB-201 and a structurally related analog of ASP-7,962, were subsequently shown to be efficacious in animal models of Cryptosporidium infection at clinically relevant doses, based on available human doses. In addition, an open-access data portal (https://reframedb.org) has been developed to share ReFRAME screen hits to encourage additional follow-up and maximize the impact of the ReFRAME screening collection.
Juvenile liver fluke stem cells, growth dynamics and therapeutics

Aaron G. Maule, Erica Gardiner, Nathan Clarke, Matt Evans, Erin McCammick, Paul McVeigh, Emily Robb, Nikki J. Marks

Parasitology & Pathogen Biology, The Institute for Global Food Security, School of Biological Sciences, Queen’s University Belfast, Belfast BT9 7BL
E-mail: a.maule@qub.ac.uk

Fasciola species parasites cause fasciolosis in animals and humans, undermining food production and causing a neglected tropical disease. Whilst flukicides are used to control infection in animals and humans, only triclabendazole is effective against both early-stage juveniles and adults; most are only effective against the latter. We have developed methods that enable the long term maintenance of growing juvenile liver fluke in vitro and whilst they do not reach sexual maturity, they do develop to display adult-like features. During extended in vitro maintenance and development, flukes are RNAi-susceptible, providing opportunities to interrogate gene function, thereby supporting early stage target validation and studies on target engagement. Liver fluke survival in vitro is dependent on the proliferation of neoblast-like stem cells. Irradiation inhibits stem cell proliferation in juvenile F. hepatica in the short term post irradiation, and has a significant effect on growth rate in the long term. We can generate single cell suspensions of F. hepatica cells that include viable proliferating cells, providing a platform for single cell analysis. We find that silencing selected stem-cell markers, as well as flukicide treatment, dramatically impacts neoblast proliferation in juveniles. Further, neoblast proliferation facilitates worm recovery from flukicide treatment, and ablating neoblast proliferation diminishes drug tolerance. The results provide evidence for a significant relationship between parasite stem cells, growth dynamics and response to therapeutics.
Abstract of Keynote Talks

**Vulnerable molecular targets in tick physiology**

Petr Kopáček¹, Jan Perner¹, Matěj Kučera¹,², Tereza Hatalová², Ondřej Hajdušek¹

Daniel Sojka¹

¹Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, České Budějovice, Czech Republic; ²Faculty of Science, University of South Bohemia, České Budějovice, Czech Republic.

E-mail: kopajz@paru.cas.cz

Ticks are ectoparasitic mites completely dependent on the host blood as their exclusive source of nutrients. A striking trait of these blood-feeders is their extreme gluttony. Ticks are capable to ingest and digest the amount of blood exceeding their weight more than hundred times. Tick adaptations to their parasitic lifestyle resulted in major physiological departures from their hosts e.g. intracellular digestion based on the network of cysteine and aspartic peptidases [1], heme auxotrophy [2], or iron metabolism [3]. An impairment of the vital processes such as control of blood digestion, heme/iron metabolism, or waste management of excessive blood diet components can be detrimental for ticks.

Beside RNAi-interference that substantially contributed to our knowledge of function of many tick molecules, the recently implemented technique of tick *in vitro* feeding represents another great tool allowing to address yet experimentally inaccessible biological questions in tick physiology [4]. Using membrane feeding, we can dissect out the essential nutritional components of blood meal diet (e.g., heme, lipids, sugars etc.) and investigate their importance in the tick development, control of blood-digestive machinery, vitellogenesis and other processes. The new discoveries in the tick physiology achieved by *in vitro* feeding may lead to the identification of novel potential targets for the development of efficient preparations and/or vaccines protecting against ticks and diseases they transmit.

The *Drosophila melanogaster* antimicrobial peptides Mtk-1 and Mtk-2 are active against the malarial parasite *Plasmodium falciparum*

**Miray Tonk**¹, Christine Pierrot², Alejandro Cabezas-Cruz³,⁴,⁵, Mohammad Rahnamaeian⁶, Jamal Khalife², Andreas Vilcinskas¹,⁶

¹Institute for Insect Biotechnology, Justus Liebig University Giessen, Germany. ²Center for Infection and Immunity of Lille (CIIL), INSERM U1019 – Université Lille Nord de France, Institut Pasteur de Lille, France. ³UMR BIPAR, INRA, ANSES, Ecole Nationale Vétérinaire d’Alfort, Université Paris-Est, Maisons-Alfort, France. ⁴Faculty of Science, University of South Bohemia, Czech Republic. ⁵Institute of Parasitology, Biology Center, Czech Academy of Sciences, Czech Republic. ⁶Fraunhofer Institute for Molecular Biology and Applied Ecology, Department of Bioresources, Germany.

E-mail: miray.tonk@agrar.uni-giessen.de

Malaria is a mosquito-borne disease affecting millions of people mainly in Sub-Saharan Africa, Asia and some South American countries. Drug resistance to first-line antimalarial drugs (e.g. chloroquine, artemisinin) is a major constrain in malaria control. Antimicrobial peptides (AMPs) have shown promising results in controlling *Plasmodium* spp. parasitemia in *in vitro* and *in vivo* infection models. AMPs are important components of the innate immunity of invertebrates and vertebrates. Currently, it is widely recognised that many organisms use AMPs as a defense system against microbial infection. They have broad spectrum antimicrobial activity against bacteria, fungi and viruses. The potential activity of AMPs against protozoan parasites is less known. In this study, we tested 10 AMPs from three different insect species: the greater wax moth *Galleria mellonella* (cecropin A–D), the fruit fly *Drosophila melanogaster* (drosocin, Mtk-1 and Mtk-2) and the blow fly *Lucilia sericata* (LSerPRP-2, LSerPRP-3 and stomoxyn) against the protozoan parasite *Plasmodium falciparum*. Only *D. melanogaster* Mtk-1 and Mtk-2 significantly inhibited the growth of *P. falciparum* at low concentrations. They could therefore be considered as leads for the development of anti-parasitic drugs targeting the clinically important asexual blood stage of *P. falciparum*. 

Abstracts of Talks
CD4+ T-cell response and regulation in acute and chronic malaria

Maria Mackroth1,2, Annemieke Abel2, Christiane Steeg2, Julian Schulze zur Wiesch1, Thomas Jacobs2

1University Hospital Hamburg-Eppendorf, Section of Infectious Diseases and Tropical Medicine, Hamburg, Germany; 2Bernhard-Nocht-Institute for Tropical Medicine, Department of Immunology, Hamburg, Germany
E-mail: tjacobs@bnitm.de

Plasmodium falciparum (Pf) malaria comprises a wide clinical spectrum, ranging from severe malaria with high lethality to asymptomatic, infection. In individuals with little exposure, Pf infection induces a strong, proinflammatory immune response which has been shown to confer protection against malaria but also contributes to severe disease. With repeated exposures, people in endemic areas develop "anti-disease immunity" which protects from clinical disease but the involved mechanisms are poorly understood. We therefore investigated the T cell regulation through coinhibitory receptors in acute and chronic malaria. Flow cytometric analysis showed high expression of the coinhibitory receptors CTLA4 and PD1 on CD4+ T cells. In-vitro stimulation revealed a distinct population of CTLA4+PD1+ CD4+ T cells which simultaneously produced IFNg and IL10. We further isolated CD4+ T cells based on surface expression of PD1 and investigated their inhibitory function. Surprisingly, CTLA4+PD1+CD4+ T cells suppressed anti-CD3/28-induced as well as plasmodial-specific T-cell proliferation. We subsequently investigated the expression of coinhibitory receptors on CD4+ T cells in Pf infected children in a holoendemic region in Ghana. We compared the expression patterns between children with different clinical pictures of infection: 1) hospitalized children with acute malaria, 2) children with uncomplicated malaria, managed as outpatients and 3) children with asymptomatic infection. Different expression patterns of coinhibitory receptors were detected in the three groups, suggesting that the CD4+ T cell response and CD4+ T cell regulation contribute to the different clinical pictures of Pf malaria.
Glucose 6-phosphate dehydrogenases of different pathogens as potential drug targets

I. Berneburg, S. Rahlfs, K. Becker

Biochemistry and Molecular Biology, Justus Liebig University, Heinrich-Buff-Ring 26-32, 35392 Giessen, Germany
E-mail: isabell.berneburg@ernaehrung.uni-giessen.de

Unicellular and multicellular parasites, which are of global concern, are showing increasing resistance to clinically used drugs. Thus, new drug targets and antiinfective agents with new mechanisms of action are urgently required. The enzyme glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme of the pentose phosphate pathway. G6PD provides NADPH for biosynthetic processes and antioxidant defence in most pathogens. In blood stages of the malaria parasite Plasmodium falciparum G6PD has been shown to be essential. After recombinant production of the enzyme, high throughput screening of about 400,000 compounds, SAR studies, and the optimization of the most promising compounds, we obtained a PfG6PD inhibitor with nanomolar in vitro and in vivo activity. Presently, we are aiming to transfer this concept to G6PDs of other parasites including Schistosoma mansoni, Leishmania donovani, and the multidrug resistant bacterium Acinetobacter baumannii. As a first step, we recombinantly produced the respective enzymes in E. coli, purified them and characterized them biochemically and kinetically. First studies with known G6PD inhibitors have been carried out; crystallization and gene knock out studies for target validation are on the way.
**Babesia proteasome as a drug target**

D. Sojka¹, M. Jalovecká¹,², L. Robbertse¹, D. Reichensdorferová¹,², D. Hartmann¹,², A. J. O’Donoghue³

¹Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, CZ-370 05 Ceske Budejovice, Czech Republic; ²University of South Bohemia, CZ-370 05 Ceske Budejovice, Czech Republic; ³Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, USA

E-mail: sojkadan@gmail.com

Although *Babesia* represent an important worldwide veterinary threat and an emerging risk to humans, these parasites have been poorly studied as compared to *Plasmodium*, their malaria-causing relative. Since the proteasome of *Plasmodium* has been validated by our collaborators as a potential target for anti-malarial drug development our experimental investigated the effect of epoxyketone (carfilzomib, ONX-0914 and epoxomicin) and boronic acid (bortezomib and ixazomib) proteasome inhibitors on the growth and survival of *Babesia*. Testing the compounds against *Babesia divergens* ex vivo revealed suppressive effects on parasite growth with activity that was higher than the cytotoxic effects on a non-transformed mouse macrophage cell line. Furthermore, we showed that the most-effective compound, carfilzomib, significantly reduces parasite multiplication in a *Babesia microti* infected mouse model without noticeable adverse effects. In addition, treatment with carfilzomib lead to an ex vivo and in vivo decrease in proteasome activity and accumulation of polyubiquitinated proteins compared to untreated control. Overall, our results demonstrate that the *Babesia* proteasome is a valid target for drug development and warrants the design of potent and selective *B. divergens* proteasome inhibitors for the treatment of babesiosis.
Druggable targets in cyclic nucleotide signaling pathways in apicomplexan parasites and kinetoplastids against disabling protozoan diseases in humans
Annette Kaiser

Medical Research Centre, University Duisburg-Essen, Hufelandstrasse 55, 45147 Essen, Germany.
E-mail: kaiser@microbiology-bonn.de

Cell signaling in eukaryotes is an evolutionarily conserved mechanism to respond and adapt to various environmental changes. In general, signal sensation is mediated by a receptor which transfers the signal to a cascade of effector proteins. The cyclic nucleotides 3′,5′-cyclic adenosine monophosphate (cAMP) and 3′,5′-cyclic guanosine monophosphate (cGMP) are intracellular messengers mediating an extracellular stimulus to cyclic nucleotide-dependent kinases driving a change in cell function.

In apicomplexan parasites and kinetoplastids, which are responsible for a variety of neglected, tropical diseases, unique mechanisms of cyclic nucleotide signaling are currently identified. Collectively, cyclic nucleotides seem to be essential for parasitic proliferation and differentiation. However, there is no genomic evidence for canonical G-proteins in these parasites while small GTPases and secondary effector proteins with structural differences to host orthologues occur. Database entries encoding G-protein-coupled receptors (GPCRs) are still without functional proof. Instead, signals from the parasite trigger GPCR-mediated signaling in the host during parasite invasion and egress. Due to the absence of G-proteins, apicomplexan parasites and kinetoplastids may use small GTPases or their secondary effector proteins and host canonical G-proteins during infection. Here, we report the feasibility of targeting cyclic nucleotide signaling pathways in these parasites to identify selective, pharmacological inhibitors.
Tim-3 blockade decreases parasitic load in acute *Trypanosoma cruzi* infection

R.I. Grote-Gálvez, T. Jacobs

Protozoa Immunology, Bernhard-Nocht-Institute for Tropical Medicine, Hamburg, Germany.

E-mail: grote-galvez@bnitm.de

Infection with the obligate intracellular protozoan parasite *Trypanosoma cruzi* (*T. cruzi*) and the resulting Chagas Disease remains the most important neglected vector-borne disease in Latin America. An initial robust CD8+ T cell response successfully controls parasite replication. However, due to unknown reasons, a complete clearance fails, which leads to parasite persistence in the tissue and subsequent chronic infection. 30% of chronic cases develop clinical Chagas Disease. Using a mouse infection model, we have found that in the acute phase of *T. cruzi* infection, T cells are modulated and show a transient upregulation of different co-inhibitory receptors on CD4+ as well as on CD8+ T-cells. The T cell immunoglobulin and mucin-domain containing-3 (Tim-3) receptor was the most significantly upregulated on CD8+ T cells and this expression correlates with a significantly reduced function of these cytotoxic cells. Using different therapeutic intervention strategies with blocking antibodies, we are exploring the effect on the clearance of parasitic reservoirs in the tissue and have found that the Tim-3 signaling axis plays an important role in regulating CD8+ T cell function. This is an important contribution towards the understanding of the immune evasion strategies induced by *T. cruzi* and identification of new potential targets of immunotherapy.
Abstracts of Talks

**Fragment-based drug discovery approach for the identification of new inhibitors of *Trypanosoma brucei* PTR1**

Pasquale Linciano\(^a\), Stefano Mangani\(^b\), Cecilia Pozzi,\(^b\) Sheraz Gul\(^c\), Anabela Cordeiro da Silva\(^d\), Rebecca Wade\(^e\), Luca Costantino\(^a\), Maria Paola Costi\(^a\)

\(^a\) Dipartimento di Scienze Farmaceutiche, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, 41100 Modena, Italy. \(^b\) Dipartimento di Biotecnologia, Chimica e Farmacia, Università di Siena, Via Aldo Moro 2 – 53100 Siena, Italy. \(^c\) Fraunhofer Institute for Molecular Biology and Applied Ecology ScreeningPort (Fraunhofer-IME SP), Schnackenburgallee 114, D-22525 Hamburg, Germany. \(^d\) IBMC - Instituto de Biologia Molecular e Celular, Universidade do Porto, Oporto, Portugal. \(^e\) Heidelberg Institute for Theoretical Studies (HITS) GmbH, Schloss-Wolfsbrunnenweg 35, 69118 Heidelberg, Germany.

E-mail: mariapaola.costi@unimore.it

According to WHO, parasitic diseases, such as African (sleeping sickness) and American (Chagas disease) trypanosomiasis and Leishmaniasis, afflict over three billion people in the world, Drugs currently in use have major limitations and there is a clear necessity to discover new leads and drugs.

Trypanosomatids lack the ability to synthesize folates de novo and are dependent on the salvage of extracellular folates. However, antifolates cannot be used in therapy of trypanosomatidic infections because dihydrofolate reductase (DHFR) inhibition is compensated by pteridine reductase-1 (PTR1). Therefore, PTR1 could be a promising target for the design and the development of new antiparasitic drugs [1]. We started a fragment-based drug design (FBDD) approach to improve the quality and the potency of PTR1 inhibitors.

The X-ray crystallography screening identified several pteridin-like fragments with affinity ranging between 10\(^{-3}\)-10\(^{-4}\) M Ki values. Fragment growth and fragment linking strategies led to the synthesis of the new inhibitors showing Ki in the 10\(^{-8}\) range. All the synthesized compounds were evaluated for their capability to inhibit parasitic PTR1 as well as other parasitic folate-dependent enzymes (TS and DHFR). All the assays have been performed through HTS technologies. Seven new crystallographic structures of the developed compounds were also obtained in ternary complexes with TbPTR1-NADPH. All the compounds have been tested against the different parasites. The present work delivered high-quality lead candidates.

Structure-based drug discovery for African sleeping sickness by targeting a subpocket in *Trypanosoma brucei* phosphodiesterase B1

Antoni R. Blaazer¹, Abhimanyu K. Singh², Ewald Edink¹, Kristina M. Orrling¹, Johan Veerman³, Toine van den Bergh³, Chimed Jansen¹, Erin Balasubramaniam², Wouter J. Mooij¹, Erik de Heuvel¹, Daniel N.A. Tagoe⁴, Jane C. Munday⁴, Hermann Tenor⁵, An Matheeussen⁶, Maikel Wijtmans¹, Marco Siderius¹, Chris de Graaf¹, Louis Maes⁶, Harry P. de Koning⁴, David Bailey⁷, Geert Jan Sterk¹, Iwan J.P. de Esch¹, David G. Brown²*, Rob Leurs¹

¹Division of Medicinal Chemistry, Universiteit Amsterdam, Amsterdam, The Netherlands; ²School of Biosciences, University of Kent, Canterbury, UK; ³Mercachem, Nijmegen, The Netherlands; ⁴Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK; ⁵Topadur Pharma AG, Schlieren, Switzerland; ⁶Laboratory for Microbiology, Parasitology and Hygiene, University of Antwerp, Wilrijk, Belgium, ⁷IOTA Pharmaceuticals, Cambridge, UK

E-mail: g.j.sterk@vu.nl

Obtaining selective inhibitors is an important therapeutic objective when targeting cyclic nucleotide phosphodiesterases (PDEs). One such PDE, *Trypanosoma brucei* PDE B1 (TbrPDEB1), is a validated drug target for the treatment of African sleeping sickness. Here, we elucidate the molecular determinants of inhibitor binding and explore the P-pocket of this enzyme as an accessible parasite-specific ligand-binding region, amenable to directed design and absent from the highly homologous human PDE off-targets hPDE4B and hPDE4D. By iterative cycles of design, synthesis, pharmacological evaluation and structure elucidation of inhibitor-bound TbrPDEB1 and hPDE4B/4D complexes, we have developed the first selective TbrPDEB1 inhibitors. Subsequent treatment of parasites with these TbrPDEB1 inhibitors reveals an increase in intracellular cAMP levels and severe disruption of *T. brucei* cellular organization, chemically validating TbrPDEB1 as a therapeutic target in trypanosomiasis. Furthermore, since all trypanosomatid PDEs are believed to possess P-pockets close to their active sites, our studies provide a generic rationale for the discovery of further selective antiparasitic PDE inhibitors.
How does chromatin regulate RNAPII transcription in *Trypanosoma brucei*?

Amelie J. Kraus¹, Jens T. Vanselow², Rasha ElBashir², Benedikt Brink¹, Christian J. Janzen³, Andreas Schlosser², T. Nicolai Siegel¹


E-mail: amelie.kraus@lmu.de

In the eukaryotic parasite *Trypanosoma brucei*, RNA polymerase II (RNAPII) transcription is not depending on canonical promoter motifs and regulation of gene expression occurs mainly through post-transcriptional mechanisms. Transcription initiates over broad transcription start regions (TSRs), which are marked by nucleosomes containing acetylated histones and the histone variant H2A.Z, both typical characteristics of eukaryotic promoter regions and associated to active transcription.

To elucidate the importance of TSR-specific chromatin organization for RNAPII transcription in trypanosomes, we characterized the acetylation pattern on TSR-nucleosomes and identified that the histone acetyltransferases HAT1 and HAT2 play a crucial role in setting up the TSR-chromatin structure. Nucleosomal rearrangements at TSRs caused strong transcriptional deregulation not only affecting initiation but also changing elongation efficiency. Our data affirm that TSR-specific chromatin composition is fundamental for transcription in trypanosomes and propose that H2A.Z functions as a regulator aligning the complex processes of RNA synthesis and maturation.
How does the histone methyltransferase DOT1B influence antigenic variation and developmental differentiation of *Trypanosome brucei*?

Nicole Eisenhuth¹, Tim Vellmer¹, Falk Butter², Christian J. Janzen¹

¹Zell- und Entwicklungsbiologie, Biozentrum, Universität Würzburg, Germany
²Institut für Molekulare Biologie (IMB), Mainz, Germany
E-mail: christian.janzen@uni-wuerzburg.de

Antigenic variation is an essential mechanism for survival of the protozoan parasite *Trypanosoma brucei* inside its mammalian host. This process is mediated by tightly controlled monoallelic expression of Variant Surface Glycoproteins (VSG) from one of 20 subtelomeric VSG expression sites (ES). We showed previously that the conserved histone methyltransferase DOT1B is involved in monoallelic expression and switching of VSG genes and developmental differentiation in African trypanosomes [1,2,3].

To better understand the mechanisms of ES regulation in *T. brucei*, we employed biochemical approaches to purify DOT1B-interacting protein complexes. Using tandem affinity purification, we identified several DOT1B-associated components. Surprisingly, one of the most abundant DOT1B-associated protein complexes was RNaseH2. The trimeric RNaseH2 complex removes single wrongly incorporated nucleotides and RNA:DNA hybrids, so-called R-loops in the genome. It has been shown recently that accumulation of R-loops destabilizes the actively transcribed ES in trypanosomes [4]. We hypothesize that DOT1B recruits the RNaseH2 complex to an active ES to remove R-loops and, thus, stabilizes transcription from this ES.

Currently, we also explore if the functions and components of DOT1 protein complexes are conserved in other kinetoplastida such as *Trypanosoma cruzi* and *Leishmania mexicana* and if DOT1 enzymes are suitable as therapeutic targets.

The common need to evade the host immune response has led to the evolution of remarkably similar survival strategies even among evolutionarily distant pathogens. One of these is antigenic variation, where an infecting organism systematically alters the identity of proteins to prevent elimination by the host immune system [1]. Antigenic variation involves mechanisms to generate large reservoirs of immunologically diverse antigens by recombination and to ensure the expression of one or few antigens at any given time. Homologous recombination and gene expression are known to be affected by spatial genome conformation and DNA accessibility [2-3].

Studying the role of genome architecture in antigenic variation has been challenging in many pathogens since both, the repetitive nature and heterozygosity of antigen arrays, have hindered a complete genome assembly. Combining long-read sequencing and conserved features of chromatin folding [4], we generated a haplotype-specific scaffold of the *Trypanosoma brucei* antigen arrays. Hi-C reveals a distinct partitioning of the genome with subtelomeric regions, harboring the repertoire of repressed antigens, fold into highly compacted compartments. Further, a combination of Hi-C, FISH, ATAC-seq and single-cell RNA-seq analyses show that deletion of histone variants H3.V and H4.V promotes the clustering of antigen-coding genes, increases DNA accessibility and drives antigen switching via homologous recombination. This suggests a molecular link between histone variants, chromatin architecture and chromatin conformation and antigenic variation [5].

Resistance formation to nitro drugs in *Giardia lamblia*: Comparative proteomics of three resistant strains and their respective wild-types

Joachim Müller\(^a\), Sophie Braga\(^b\), Manfred Heller\(^b\), Norbert Müller\(^a\)

\(^a\)Institute of Parasitology, Vetsuisse Faculty, University of Berne, Länggass-Strasse 122, CH-3012 Berne, Switzerland; \(^b\)Proteomics & Mass Spectrometry Core Facility, Department for BioMedical Research (DBMR), University of Bern, Freiburgstrasse 15, CH-3010 Bern.

E-mail: joachim.mueller@vetsuisse.unibe.ch

Metronidazole and other nitro compounds are the therapy of choice against giardiasis. As a consequence, resistance formation to metronidazole and to other nitro drugs such as nitazoxanide occurs more and more frequently. Stable metronidazole- and nitazoxanide-resistant *Giardia lamblia* trophozoite lines are used as model systems to study the biochemical basis of resistance formation. In order to answer the question whether resistance formation to nitro drugs follows a common pattern, we performed a comparative shotgun mass spectrometry analysis of three *Giardia lamblia* strains resistant to both metronidazole and nitazoxanide and their corresponding wild-type strains.

Depending on the strain and the nitro drug, more than 200 to 500 differentially expressed proteins were identified, but there were no common patterns across strains and drugs. Only one protein, the hypothetical protein p34701, was higher in all wild-types on all drugs than in the resistant strains, and there was no common protein up-regulated in the resistant strains. All resistant strains underwent antigenic variation involving variant surface proteins or cysteine rich proteins depending on strain and nitro compound. Concerning nitro reduction, our results suggest the existence of distinct strategies for each drug and each strain.

Taken together, resistance to nitro drugs in *G. lamblia* is not correlated with a specific pattern of differentially expressed resistance marker proteins.
The necessity for the development of an axenic *in vitro* mass cultivation system for *Cryptosporidium*

Panagiotis Karanis

University of Cologne, Faculty of Medicine, Center of Anatomy, Cologne, Germany
E-mail: panagiotis.karanis@uk-koeln.de

The major limitation in *Cryptosporidium* research remains the failure of long-term propagation and the increase in high yields of any asexual and sexual developmental stages, including oocysts. The axenic in vitro mass cultivation *Cryptosporidium* isolates and the propagation of life cycle stages that are responsible for causing disease in an infected host are still critical issues. Success in this effort will represent an ultimate essential step towards drug development against *Cryptosporidium* and to control cryptosporidiosis. Several advances and system improvements have also been reported in the last decade. However, the process has not yet been reproduced by other researchers or it has not been developed for routine use. The formidable task of cryptosporidiosis disease control will not be accomplished without the development of an effective in vitro culture system.

In spite of the fact that microscopic visualization is a limitation of in vitro cultivation studies, it has been confirmed that *Cryptosporidium* could also develop outside of its host and it also indicated that exclusive endogenous development in the host intestine is not necessary for this parasite to complete its life cycle. Electron microscopy studies have shed light not only on the morphology at the ultra-structural level of the emerging stages but also on the processes during which they transform into other stages. We report on: a) the fine structure of asexual, sexual stages and sporogony development in *in vitro* axenic culture; c) the ultrastructural similarities between *C. parvum* and gregarines; d) how it is possible to complete the necessary effective in vitro mass cultivation system for *Cryptosporidium* in established culture system.

The ability to reproduce *Cryptosporidium* strains in vitro and also the life cycle stages that are responsible for causing diseases in infected hosts will accelerate the discovery of anti-cryptosporidial drugs for effective therapy against cryptosporidiosis.
Glutamate carboxypeptidases 2 (GCP2), also known as PSMA or NAALADase in mammals, is a membrane-bound dizinc metallopeptidase that belongs to the M28(B) peptidase family. Unusual feature of this family is based on the involvement of aminopeptidase as well as carboxypeptidase activities. GCP2 is ubiquitously expressed across all phyla from single cell yeasts through plants to vertebrates. Despite the roles of the enzymes are not fully elucidated, GCP2 serves as a target of pharmacological interventions in the field of neurodegenerative diseases and cancers with many clinical trials ongoing. Model organisms used in our study include platyhelminths and nematodes, here represented by *Schistosoma mansoni* and *Caenorhabditis elegans*, respectively. Despite their phylogenetical distance from humans and between each other; there is a reason to investigate their GCP2 orthologs as they represent organisms with relatively simple body organization with well-characterized genomes. Therefore, we selected them in order to investigate their GCP2 orthologs as potential targets for therapeutic interventions, and as well as instrumental molecules helping to elucidate their roles not only in studied organisms. Our localization studies, reverse genetic and phylogenetic analyses imply specific functions of GCP2 orthologs in platyhelminths and nematodes. We are currently employing metabolomics and multiplex substrate profiling in order to reveal specific proteolytic activities, sensitivities to range of specific GCP2 inhibitors and particular biological functions.
Identification and evaluation of peptidases of the blood fluke

Schistosoma mansoni as drug targets

M. Horn¹, P. Fajtova¹, A. Jilkova¹, M. Chanova², R. Houstecka¹, C. R. Caffrey³, M. Mares¹

¹Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo n. 2, Prague, 16610, Czech Republic; ²Institute of Immunology and Microbiology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Katerinská 32, Prague CZ, 128 00, Czech Republic; ³University of California San Diego, Center for Discovery and Innovation in Parasitic Diseases, Skaggs School of Pharmacy and Pharmaceutical Sciences, 9500 Gilman Drive, La Jolla, CA 92093, USA

E-mail: horn@uochb.cas.cz

Schistosomiasis (bilharziasis) is a global parasitic infection with more than 240 million people infected and 750 million people at risk. It is caused by Schistosoma flatworms that live in the bloodstream. Current treatment relies on one drug, and no effective vaccine has yet been developed. Proteolytic enzymes (peptidases) help the parasite to survive in the mammalian host, allowing the schistosome to invade, feed, grow, reproduce, and manipulate the immune system. Thus, proteases are considered as promising target molecules for the development of new therapeutic strategies against schistosomiasis.

Our work is focused on the evaluation of new drug targets from the degradome of adult worms and schistosomula of S. mansoni. Using functional proteomics and chemical genomics, we have identified a set of peptidases important for parasite survival; namely, tegumental prolyl oligopeptidase and digestive cathepsins C and D. These peptidases were prepared as recombinant enzymes, functionally characterized, and effective inhibitors were developed as templates for anti-schistosomal drugs.
Biarylalkylcarboxylic acid derivatives as potential antischistosomal agents

A. M. Peter Ventura¹; C. G. Grevelding²; M. Schlitzer¹

¹Institut für Pharmazeutische Chemie, Fachbereich Pharmazie, Philipps-Universität Marburg, Marbacher Weg 6, D-35032 Marburg, Deutschland; ²Institut für Parasitologie, BFS, Justus-Liebig-Universität Giessen, Schubertstraße 81, D-35392 Giessen, Deutschland.

E-mail: Peterven@staff.uni-marburg.de

The parasitic disease schistosomiasis rose much concern over the past few years. As treatment of this disease is mainly performed by the drug Praziquantel, fear of upcoming resistance is increasing. Moreover, first cases of reduced sensibility of Praziquantel against the parasites were reported, underlining the urgency of the development of new drugs [1]. In this regard, the schistosomal aldose reductase has been identified to be a potential target for new antischistosomal agents [2, 3]. Therefore, human aldose reductase inhibitors [4-5] of our group were tested in vitro on Schistosoma mansoni couples, showing an acceptable antischistosomal activity. From these investigations a new class of inhibitors (biarylalkylcarboxylic acids) was born. Derivatisation of this substance class led to a significantly improved activity against Schistosoma mansoni couples. Phenotypes such as decreased pairing stability, motility and egg production were observed. These promising results take us one step further in combating schistosomiasis.

**Schistosoma mansoni** Mitogen Activated Protein Kinases: Validation as potential targets and screening of the m Nottingham Managed Chemical Compound collection (MCCC) for inhibitors using a novel universal kinase binding assay

Bernardo Pereira Moreira\(^1,2\), Camilla Valente Pires\(^1,2\), Tom Armstrong\(^3\), Izabella Cristina Andrade Batista\(^1,2\), Naiara Cristina Clemente dos Santos Tavares de Paula\(^1,2\), Lodewijk V. Dekker\(^1\), Marina de Moraes Mourão\(^2\), Franco H. Falcone\(^1\)

\(^1\) School of Pharmacy, Division of Molecular Therapeutics and Formulation, University of Nottingham, Nottingham, United Kingdom; \(^2\) Instituto de Pesquisas René Rachou, Fundação Oswaldo Cruz - FIOCRUZ, Belo Horizonte, Minas Gerais, Brazil; \(^3\) School of Chemistry, University of Nottingham, Nottingham, United Kingdom

E-mail: franco.falcone@nottingham.ac.uk

Protein kinase inhibitors (PKIs) are in use for a variety of human diseases, but have also been suggested for the treatment of parasitic infections, such as cryptosporidiosis or schistosomiasis, repurposing existing human PKIs.

Our work focuses on *Schistosoma mansoni* Mitogen Activated Protein Kinases (SmMAPK) as potential targets for PKIs against this important helminthic neglected tropical disease. Previous work using RNAi has demonstrated that SmMAPKs play important roles in parasite development and fecundity. In order to screen for potential new drug leads using the University of Nottingham Managed Chemical Compound Collection (MCCC; 80,000 compounds), we established a modular workflow, consisting of a) recombinant expression and purification of SmMAPKs b) the development of a universal ATP binding inhibition assay and c) an *in silico* bioinformatic pipeline for screening and ranking the ability of compounds to block the ATP binding site using the predicted three-dimensional structures of the SmMAPKs (SmERK1, SmERK2, SmJNK, Smp38), followed by *in vitro* validation of the best hits.

Recombinant expression of SmJNK was achieved using a baculovirus-based expression in *Spodoptera frugiperda* Sf9 insect cells. This system resulted in the production of functional, correctly folded (ATP-binding) MAPK. After optimising and validating the screening system using protein Kinase A and a known inhibitor, we identified PKIs for SmJNK, which will now be further tested *in vitro* and *in vivo*. 

28
Dithiocarbamates as potential agents against schistosomiasis

G. A. Rennar¹, C. G. Grevelding², M. Schlitzer¹

¹Institut für Pharmazeutische Chemie, Philipps-Universität Marburg; ²Institut für Parasitologie, Justus-Liebig-Universität Gießen
E-mail: georg.rennar@pharmazie.uni-marburg.de

Schistosomiasis, also known as bilharzia, is a chronic parasitic disease infecting more than 250 million people. At least 200,000 deaths per year are due to this disease. Beyond Malaria, it is the second most important neglected tropical disease worldwide occurring in over 70 countries in tropical and subtropical regions [1].

Due to the lack of a vaccine, the therapy is restricted to a single drug, called Praziquantel. But there have been first reports of low efficacy in laboratory and field studies. Therefore, the fear of drug resistance encourages the search for novel anthelmintic drugs against schistosomiasis [2-4].

Dithiocarbamates were identified as anthelmintic compounds from a screening with disulfiram which is a known inhibitor of the enzyme aldehyde dehydrogenase. It was recognized that disulfiram also disintegrates the surface structure of schistosomes, the tegument, leading to the death of the parasites. Our hypothesis is that the dithiocarbamate structure is the important functional moiety. Thus, we synthesized more than 350 dithiocarbamate compounds that show significant effects on adult schistosomes in vitro.

Drug screening on live schistosomes for anti-parasitic compound discovery

H. Haas¹, M. Sombetzki², P. Gribbon³, A. v. Diepen⁴, C. H. Hokke⁴, G. Schramm¹,⁵

¹helminGuard, Sülfeld/Borstel, Germany; ²Department for Tropical Medicine and Infectious Diseases, University Medical Center, Rostock, Germany; ³IME ScreeningPort, Hamburg, ⁴Leiden University Medical Center, The Netherlands, ⁵Experimental Pneumology, Research Center Borstel, Germany.

E-mail: hhaas@helminguard.de

Parasitic worm infections are the cause behind serious health problems and economic damage worldwide. Mass treatment of humans and animals has led to rising numbers of resistances to anthelminthic drugs.

The in vitro culture of parasitic worms (Schistosoma mansoni and S. haematobium) established at helminGuard serves as a technical platform for identifying new anthelminthic drugs. In contrast to target-based procedures, drug screening on live worms in a host-like environment reveals compound effects in real time directly on the pathogen. This allows the exclusion of irrelevant compounds and may help in reducing down-stream in vivo experimentation. In vitro-grown schistosome larvae, juveniles and adults were exposed to compounds from various drug libraries to identify anti-schistosomal agents.

The toxic effects on schistosomes varied between drugs/groups: there were early vs. late effects, hyper-activity vs. paralysis, shrinkage vs. extension, empty vs. filled guts, circular contractions vs. ballooning of the worms. Screening of approved drugs confirmed that many anti-malarial compounds, namely quinine and artemisinin derivatives, are toxic for schistosomes suggesting commonalities between both parasites.

We expect that due to shared pathways among parasitic worms, new anthelminthics have the potential to protect against a variety of helminth species in a similar manner to praziquantel, the present drug of choice against schistosomiasis, which is active against many trematode and tape worm species.
A novel cell-free method to culture *Schistosoma mansoni* from cercariae to juvenile worm stages for *in vitro* drug testing

Sören Frahm, Anisuzzaman, Fabien Prodjinotho, Nermina Vejzagić, Admar Verschoor, Clarissa Prazeres da Costa

*Institute for Microbiology, Immunology and Hygiene, Technische Universität München, Trogerstraße 30, 81675 Munich, Germany; Department of Parasitology, Bangladesh Agricultural University, Mymensingh-2202, Bangladesh; Institute for Systemic Inflammation Research, Universität zu Lübeck, 23538 Lübeck, Germany*

¶ these authors contributed equally to this work
● these authors contributed equally to this work

E-mail: nermina.vejzagic@tum.de

The anthelminthic treatment against schistosomiasis is limited and relies almost exclusively on a single drug, praziquantel. Even though praziquantel is potent in killing adult worms, it has been shown to have limited activity against earlier developmental stages. Current *in vitro* drug screening strategies depend on newly transformed schistosomula for initial hit identification, thereby limiting sensitivity to new compounds predominantly active on later developmental stages. This study aimed to establish a highly standardized, straightforward and reliable culture method to generate and maintain advanced larval stages *in vitro*. Cercariae were mechanically transformed into skin stage schistosomula and successfully cultured under cell- and serum-free conditions for up to four weeks. Under these conditions, larval development halted at the lung stage. Addition of human serum propelled further development into juvenile worms within eight weeks. Skin and lung stages, as well as juvenile worms (late liver stage), were tested with praziquantel, oxamniquine, mefloquine and artemether. Our findings showed stage-dependent differences in larval susceptibility to the tested drugs. The phenotype of juvenile worms, when exposed to reference drugs, was comparable to previously published works for *ex vivo* harvested adult worms. This *in vitro* assay can help reduce reliance on animal experiments in the search for new anti-schistosomal drugs and provide a platform for the investigation of the host protein- or cell-mediated effects on the parasite’s development.
When non-specific beats specific treatment: Behind the scene of T-cell mediated hepatic fibrosis in *Schistosoma mansoni* infection.

M. Sombetzki¹, F. Winkelmann¹, A. Rabes¹, N. Koslowski¹, M. Bischofsberger¹, M. Trauner², E. C. Reisinger¹

¹Department of Tropical Medicine and Infectious Diseases, University Medical Center, Rostock, Germany; ²Hans Popper Laboratory of Molecular Hepatology, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Austria

E-mail: martina.sombetzki@uni-rostock.de

Liver fibrosis represents an overwhelming wound-healing process, characterized by excessive deposition of extracellular matrix, to chronic injury which is frequently driven by inflammation [1]. *Schistosoma mansoni* infection is one of the leading causes of hepatic fibrosis and portal hypertension worldwide. In schistosomiasis, hepatic fibrosis is initiated by a vigorous granulomatous response to tissue entrapped parasite eggs that is mainly orchestrated by counterregulatory Th1, Th2 and Treg cytokines. Increased hepatic resistance to blood flow and subsequently portal hypertension with its sequels, such as ascites and esophageal varices, characterize the clinical picture of hepatic schistosomiasis [2]. Although anthelminthic therapy is effective to treat *S. mansoni* infection, organ injury and portal hypertension may persist, reflecting the urgent need for novel treatment strategies for *S. mansoni*-induced liver fibrosis.

During the last years, we performed different experimental setups to treat or prevent hepatic fibrosis in a murine model of *S. mansoni* infection with varying degrees of success. Specific blocking of IL-11 as important profibrotic mediator failed to reduce hepatic fibrosis in *S. mansoni* infection [3]. Pre-infection with female schistosomes displayed a strong anti-fibrotic effect that was presumed to be CTLA-4 depended [4]. Subsequent CTLA-4 administration was sufficient to prevent but not to treat hepatic fibrosis. Solely, non-specific treatment with the artificial bile acid 24-nor-ursodeoxycholic acid exhibited an auspicious therapeutic activity [5].

Deorphanizing G protein-coupled receptors in *Schistosoma mansoni* by yeast two-hybrid analyses

Oliver Weth¹, Zhigang Lu², Steffen Hahnel¹, Christoph G. Grevelding¹

¹Institute for Parasitology, Justus Liebig University Giessen, Germany; ²Wellcome Trust Sanger Institute, Wellcome Genome Campus, Hinxton, United Kingdom

E-mail: oliver.weth@vetmed.uni-giessen.de

Schistosomiasis is a neglected tropical disease caused by platyhelminths of the genus *Schistosoma*. The disease has global impact on human and animal health. According to the WHO, approximately 600 million people live in endemic areas, of which > 200 million require treatment [1]. Schistosomes are the only platyhelminths that have evolved separate sexes and they exhibit a unique reproductive biology because the female's sexual maturation depends on a constant pairing-contact with the male. Because medical treatment is based on a single drug, praziquantel, there is urgent need for the development of alternative control strategies.

Due to their proven druggability, G protein-coupled receptors (GPCRs) are promising targets for anthelmintics. However, to identify candidate receptors, a deeper understanding of GPCR signaling in schistosome biology is essential. Comparative transcriptomics of paired and unpaired worms and their gonads revealed 39 differentially regulated GPCR genes putatively involved in neuronal processes [2-3]. In general, the diversity among GPCRs and their integral membrane topology make it difficult to characterize and deorphanize these receptors. Here, we used two innovative yeast two-hybrid assays to associate neuropeptide ligands with their cognate receptors. These methods allowed us to identify first GPCR targets of neuropeptides, which are differentially expressed in a pairing-dependent manner. Besides their value for basic research, providing first insights into the participation of GPCRs/neuropeptides in schistosome male-female interaction, the results can also be exploited for applied purposes.

[1] www.who.int/news-room/fact-sheets/detail/schistosomiasis
Aldehyde dehydrogenases as potential drug targets in the liver fluke Fasciola hepatica

H. Houhou¹, G. Rennar², P. Mäder², M. Hardt³, A. Grünweller², M. Schlitzer², C. Strube⁴, A. Maule⁵, C.G. Grevelding¹, S. Häberlein¹

¹Institute of Parasitology, BFS, Justus Liebig University Giessen, Germany; ²Institute of Pharmaceutical Chemistry, Philipps University Marburg, Germany; ³Biomedical Research Center Seltersberg - Imaging Unit, Justus Liebig University Giessen, Germany; ⁴Institute for Parasitology, Centre for Infection Medicine, University of Veterinary Medicine Hannover, Germany; ⁵Parasitology & Pathogen Biology, The Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, UK

E-mail: simone.haeberlein@vetmed.uni-giessen.de

The liver fluke Fasciola hepatica is a cosmopolitan parasitic flatworm causing zoonotic disease in humans and economic losses in livestock. Because of the spread of resistance against the commonly used drug triclabendazole, there is an urgent need to find alternative treatment options.

Aldehyde dehydrogenases (ALDHs) are involved in cellular detoxification of otherwise harmful aldehydes. We found that two ALDH-orthologs are expressed in all intra-mammalian stages of F. hepatica: newly excysted juveniles, immature and adult flukes. In all stages, the approved drug disulfiram, an ALDH inhibitor, reduced motility in vitro as quantified by ImageJ-based video analysis. A similar reduction of motility was found in preliminary knock-down experiments using RNAi against both ALDH-orthologs.

In situ hybridization revealed gastrodermal ALDH expression, and disulfiram treatment caused a constriction of the intestine as revealed by confocal microscopy of TRITC-phalloidin stained flukes. As the effective concentration of disulfiram was high (20 - 100 µM), derivatives of disulfiram were chemically synthesized to improve efficacy. An imidazole-derivative that lacked cytotoxicity at 100 µM strongly reduced motility of some stages at 2-5 µM and, in some cases, was lethal.

Our findings suggest that ALDHs are interesting target molecules and disulfiram a promising basis for the design of novel multi-stage anti-fasciolid compounds. This may lead to alternatives not only for the control of Fasciola but also for other parasitic helminths expressing ALDH-orthologs.
**Echinococcus stem cells and the development of novel drugs against alveolar echinococcosis**

K. Brehm¹, K. Stoll¹, U. Koziol¹, M. Bergmann¹, S. Förster¹, C. Dissous²

¹Institut für Hygiene und Mikrobiologie, Universität Würzburg, Würzburg, Germany; ²Institute Pasteur de Lille, Lille France.

E-mail: kbrehm@hygiene.uni-wuerzburg.de

Alveolar echinococcosis (AE) caused by the metacestode stage of the cestode *Echinococcus multilocularis* is a potentially lethal zoonosis with very limited treatment options. Current chemotherapy against echinococcosis relies on benzimidazole (BZ) treatment, which is parasitostatic only and has to be given life-long. We provide evidence that BZ primarily act on differentiated cells of the parasite whereas the germinative (stem) cell population of *E. multilocularis* is largely resistant to BZ. This is likely due to the stem cell-specific expression of a beta-tubulin isoform with limited affinity to BZ. Since parasite proliferation crucially depends on the parasite’s stem cell system, these data provide for the first time a cellular and molecular explanation for the high recurrence rates of AE upon BZ chemotherapy and underscore the need to target the *E. multilocularis* stem cell system for effective chemotherapy.

To this end we recently concentrated on tyrosine kinases of the FGF receptor family and on MAPK cascade components that are expressed in *Echinococcus* stem cells. We show that host FGF stimulates parasite development and that the parasite’s FGF receptor kinases are able to functionally intertact with host FGF. We also demonstrate that the FGF receptor specific drug BIBF 1120 (Vargatef) inhibits *Echinococcus* FGF receptor kinases and parasite stem cells. We also characterized a novel MAPK cascade module that is active in differentiating parasite stem cells and transmits signals from receptor tyrosine kinases via a MEKK1 ortholog to the *Echinococcus* JNK ortholog. Interestingly, the JNK inhibitor SP600125 had only limited activities against differentiated cells of the parasite but led to depletion of stem cells from metacestode vesicles and prevented the development of parasite vesicles from stem cell cultures. We thus propose the *Echinococcus* FGF receptor kinases and the JNK cascade as promising drug targets for the development of novel drugs which, in combination with BZ, could lead to metacestode inactivation in AE patients.
Identification of novel drug targets in *Echinococcus multilocularis* by metabolomics

Dominic Ritler¹, Reto Rufener¹, Jia V. Li², Urs Kämpfer³, Claudia Bühr³, Stefan Schürch³, Britta Lundström-Stadelmann¹

¹Institute of Parasitology, Vetsuisse Faculty, University of Bern, Switzerland
²Faculty of Medicine, Department of Surgery & Cancer, Imperial College London, United Kingdom
³Department of Chemistry and Biochemistry, University of Bern, Switzerland

E-mail: Britta.lundstroem@vetsuisse.unibe.ch

Alveolar echinococcosis (AE) is caused by the metacestode of the zoonotic parasite *Echinococcus multilocularis*. Current chemotherapeutical treatment of AE relies on benzimidazoles, but these compounds do not act parasiticidal, often have to be taken life-long and can cause adverse effects. In some individuals, benzimidazoles are inactive or cause toxicity, leading to treatment discontinuation. Alternatives to benzimidazoles are needed.

*E. multilocularis* is highly dependent on nutrients from its host and this could offer new ways for targeting the parasite. To perform metabolic foot printing, consumption and release of small metabolites by the metacestode of *E. multilocularis in vitro* were analyzed by nuclear magnetic resonance (NMR) spectroscopy. Results were confirmed by independent experiments and enzyme-based methods. Interestingly, the amino acid threonine was highly consumed by the *E. multilocularis* metacestode. *In vitro* experiments showed that parasite growth was accelerated by L-threonine. However, the high threonine-consumption could not be explained by incorporation into proteins. Preliminary experiments showed increased parasite respiration upon addition of threonine to metacestodes, which might indicate the use of this amino acid in energy metabolism. Currently, experiments with radiolabeled threonine are ongoing to track down the pathways through which threonine is consumed by *E. multilocularis*. Targeting of the threonine metabolism could offer novel ways to starve the parasite without harming the host.
Screening of the MMV Pathogen Box reveals the cytochrome $bc_1$ complex as a drug target in *Echinococcus multilocularis*

**Reto Rufener, Raphael Zurbriggen, Luca Dick, Dominic Ritler, Andrew Hemphill, Britta Lundström-Stadelmann**

Institute of Parasitology, University of Bern, Switzerland  
E-mail: britta.lundstroem@vetsuisse.unibe.ch

Alveolar echinococcosis (AE) is a zoonotic disease with a high lethality, caused by metacestodes (secondary larvae) the fox tapeworm *Echinococcus multilocularis*. Current chemotherapeutic treatment options rely on benzimidazoles, which have limited curative capabilities and occasionally cause severe side effects.

Metacestodes and isolated parasite cells can be cultivated *in vitro*, and these cultures were used to screen the Medicines for Malaria Venture (MMV) Pathogen Box. The Pathogen box is a library of 400 small molecules that are active against a wide range of different pathogens. Selected compounds were further characterized and their IC$_{50}$ values against parasite metacestodes and cells, as well as their toxicity against mammalian cells were defined. The two compounds with the most promising properties were the anti-theilerial drug buparvaquone and the endochin-like quinolone ELQ-400. Both buparvaquone and ELQ-400 have been shown to be potent inhibitors of the cytochrome $bc_1$ complex in the oxidative phosphorylation of apicomplexan parasites. Using a Seahorse XFp Analyzer, we demonstrated that the cytochrome $bc_1$ complex is also a direct target of buparvaquone in *E. multilocularis*. Moreover, buparvaquone was tested *in vivo*, but failed to reduce the parasite burden in infected animals. Currently, we are testing different ELQ-derivatives regarding their activities and mode of action in *E. multilocularis*. 
Traditionally, haem has been recognised as a cytotoxic molecule that parasites need to eliminate or detoxify in order to survive. Recent evidence, however, indicates that some lineages of parasites have lost genes encoding enzymes specifically involved in haem biosynthesis. Such parasites need to acquire and utilise haem originating from their host animal, making it an indispensable molecule for their survival. In multicellular parasites, host haem needs to be systemically distributed throughout their bodies to meet the haem demands in all cell and tissue types. Host haem also gets deposited in parasite eggs, enabling embryogenesis and reproduction. Interference with the acquisition and distribution pathways clearly impairs their viability and fecundity. Characterisation of the proteins participating in the haem homeostasis network might lead to identification and validation of novel targets against these parasites.
Predictive models in anti-parasite drug discovery: from bench (through animal cage) to bedside

A.I. Olías-Molero, J. Mª Alunda

Department of Animal Health, ICPVet group, Faculty of Veterinary Medicine, Complutense University of Madrid, Madrid, Spain; Translational Research on Leishmaniasis, Instituto de Investigación “Hospital 12 de Octubre”, Madrid, Spain
E-mail: jmalunda@ucm.es

Successful drug discovery and development are probably better described as the results of the complex interaction among several scientific and technical disciplines (e.g. organic and medicinal chemists, pharmacologists, toxicologists) and not the as the happy ending of a lineal process, the so-called drug pipeline. Empirical selection of antiparasitic agents is risky and failure is a frequent outcome. Target-based selection with powerful methodologies to screen huge numbers of molecules (e.g. High Throughput Screening, HTS) and increased knowledge on biochemistry and physiology of parasites have not yet rendered the anticipated results, and attrition rates still are very high. Thus, for many parasitic diseases affecting humans and domestic animals, including zoonotic infections, current chemotherapy is at least limited.

Several factors have been incriminated in this inefficiency, including more restrictive regulations, inadequate drug selection and screening procedures, narrowness of the chemical space explored, among others. Whatever being the approach followed to identify potential drugs reliable models are needed to explore their toxicity and efficacy before going to the actual species, humans or non-human animals, in which the drugs are used. By economic and ethical constraints, experimental models tend to be as simple as possible. This selection is justified provided the models are accurate and predictive.

In our view, there are some aspects of antiparasitic drug discovery in which improvements should be made. We will focus on the value of phenotypic screening, establishment of predictive animal models in preclinical phases, both for pharmacology and efficacy studies, and high contents evaluation of toxicity and efficacy of potential drugs. Specific differences in pharmacokinetics and biodistribution of marketed antiparasitic drugs, role of parasite-induced pathophysiology, need of professional advice when testing efficacy in animal models of parasitic diseases (i.e. leishmaniasis) and other effects of surrogate animal models on drug selection will be considered.
On the development of metal-based drugs as antiparasitic agents

Carsten A. Vock¹,² and Andrew Hemphill³

¹Department of Food Sciences, Faculty of Life Sciences, University of Vienna, Vienna, Austria; ²Faculty of Chemistry, University of Vienna, Vienna, Austria; ³Institute of Parasitology, Vetsuisse Faculty, University of Berne, Berne, Switzerland

E-mail: carsten.vock@univie.ac.at

Since the discovery of cisplatin in 1965 by Rosenberg et al. [1], metal-containing chemical compounds have become a very important therapeutic option for the treatment of a variety of different forms of cancer. Ruthenium complexes are - besides platinum - perhaps the second most important type of metal-based cytostatics being in development [2] or already brought to clinical use [3]. However, the prominence and widespread clinical use of anticancer agents like cisplatin, carboplatin and oxaliplatin slightly covers the fact that metal-based drugs have also been studied extensively for their potential use as antiparasitics, in particular for the treatment of tropical diseases like malaria [4], Chagas disease and leishmaniasis [5]. A famous example is the iron-containing quinine derivative ferroquine, developed by Biot, Brocard et al. [6]. Our research is focusing on non-tropical parasitic diseases being of importance in moderate climate regions like e.g. Central Europe. We were the first to investigate the toxic effects of ruthenium complexes against Echinococcus multilocularis, Toxoplasma gondii and Neospora caninum parasites [7,8]. Therefore, the presentation will comprise a short overview of our work and of new developments regarding the treatment of diseases caused by these types of pathogenic parasites.

The cellular RNA helicase eIF4A is required for unwinding RNA secondary structures in 5´-UTRs of mRNAs during translation initiation. Many viruses also require this enzyme for their viral protein synthesis. The natural plant compound silvestrol is a potent and specific inhibitor of eIF4A and shows in our experiments broad-spectrum antiviral activity as well as low cytotoxicity in non-infected primary cells (selectivity indices > 100) [1-5]. Since eIF4A inhibitors could be isolated from different marine and terrestrial eukaryotes, the inhibition of eIF4A may be a kind of “Achilles heel” for viruses.

We are currently validating eIF4A as a new antiviral and also antiplasmodial target. We also started to investigate the structural and sequence requirements that mediate silvestrol sensitivity. We found that position, length and GC-content of viral RNA hairpins as well as poly-purine sequences affect eIF4A-dependency.

In addition to silvestrol, the identification of effective silvestrol analogs, which are readily accessible to chemical synthesis, is an important goal of our research. In particular, the silvestrol analog CR-31-B, which can be synthesized as an active (-) and an inactive (+) enantiomer [6], shows similar antiviral activity and CC50 levels as silvestrol. Currently, we are trying to crystallize and co-crystallize eIF4A in order to explore the chemical space for synthesis of new eIF4A inhibitors on structural-based data.

Illuminating the involvement of lipids in coronavirus replication

Christin Müller¹, George Kokotos², Dominik Schwudke³, Stephan Pleschka¹, John Ziebuhr¹

¹Institute of Medical Virology, Justus Liebig University Giessen; ²Department of Chemistry, National and Kapodistrian University of Athens; ³Bioanalytical Chemistry, Research Center Borstel.

E-mail: christin.mueller@viro.med.uni-giessen.de … john.ziebuhr@viro.med.uni-giessen.de

Viruses as obligate intracellular parasites have evolved a plethora of strategies to manipulate host cell (including lipid) metabolism in order to maximize their replication. Cellular membranes and their lipid components are utilized in nearly all steps of the viral life cycle, e.g. virus attachment and entry, intracellular transport, genome replication and assembly.

Similar to other positive-strand RNA viruses, coronaviruses have been reported to remodel intracellular host membranes early after virus entry, resulting in the formation of so-called replicative organelles (ROs), where viral replication and transcription take place. To date, the formation of these membranous structures is not well understood and the roles of specific cellular factors, structural rearrangements of intracellular membranes and their lipid composition remained largely unknown.

In this study, we investigated possible roles of specific lipids and lipolytic enzymes in the coronaviral life cycle (especially during RO formation) using shotgun lipidomics. The data suggest ceramides and specific lysophospholipids (the latter being mainly produced by cytosolic phospholipase A2α [cPLA2α]) play important roles in the production of ROs. The present and a previous study also revealed that inhibition of cPLA2α activity causes replication defects of other +ssRNA viruses (e.g. MERS-CoV, HCV[¹], DENV[¹]) that all employ virus-induced ROs. Our data lead us to suggest that inhibition of cPLA2a potentially provides new options for the development of broadly acting antiviral drugs.

Curiosity is in our DNA. It inspires us to answers questions, that have not yet been asked. As we look to the future, we can only imagine the breakthroughs it will make possible.

Can you?

Discover more:  
merckgroup.com  
curiosity.merckgroup.com
Abstracts of Posters

**P1**

**Optimization of a phenotypic hit, NPD-2975, for the African sleeping sickness**

Y. Zheng¹, A. Matheeussen², M. Siderius¹, GJ Sterk¹, Louis Maes², G. Caljon², Rob Leurs¹

¹Division of Medicinal Chemistry, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; ²Laboratory for Microbiology, Parasitology and Hygiene, University of Antwerp, Wilrijk, Belgium.

E-mail: y.z.zheng@vu.nl

In our consortium PDE4NPD, in search for novel potential treatments of several Neglected Parasitic Diseases, we followed a two-pronged approach: SBDD based on parasitic phosphodiesterase inhibition and a phenotypical approach by screening on several parasites _in vitro_. During these efforts, we found, phenotypically, a class of pyrazolopyrimidinones with good efficacy against the parasite _Trypanosoma brucei_, the causative agents of the African sleeping sickness; pIC₅₀ _in vitro_ between 10 and 100 nM. Optimization within this chemical class resulted in a lead compound, NPD-2975, with efficacy in several mouse models after oral application. In this poster we describe our efforts for optimization on potency, PK properties and tolerability together with the results in animal models.
**P2**

Towards specific treatment of babesiosis based on selective proteasome inhibition

L. Robbertse\(^1\), M. Jalovecká\(^{1,2}\), D. Reichensdörferová\(^{1,2}\), O’Donoghue A.J.\(^3\), D. Sojka\(^1\)

\(^1\)Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, CZ-370 05, Ceske Budejovice, Czech Republic; \(^2\)Faculty of Science, University of South Bohemia, CZ-370 05, Ceske Budejovice, Czech Republic; \(^3\) Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, USA

E-mail: luise.robbertse@paru.cas.cz

*Babesia* represents an emerging worldwide medicinal threat yet remains in the shadow of research interest to *Plasmodium*, its malaria-causing relative. Currently, human babesiosis is treated with antibiotics and antimalarials but toxic effects, relapses due to resistance, and the lack of drug specificity call for a rapid improvement in therapeutic options. The *Plasmodium* proteasome is a promising drug target, since its inhibition leads to selective elimination of even artemisinin resistant strains [1]. Lately, our team has validated *Babesia* proteasome as a novel target for selective therapy [2]. To design novel selective inhibitors, substrate specificity profiling of the *Babesia* 20S proteasome catalytic core needs to be performed and herein we discuss the optimized preceding steps of *Babesia* proteasome isolation and purification. These approaches include: (i) ubiquitin affinity-based purification utilizing an endogenous ubiquitin-like domain (RAD23) and a ubiquitin interactive motif protein (RPN10); (ii) immunoprecipitation of the *Babesia* proteasome using a commercial antibody (20S alpha and beta subunit-specific) and (iii) a two-step ion exchange (DEAE-Sepharose) and size exclusion (Sepharose 6) chromatography. In this work we correlate these approaches to the resultant activity of the *Babesia* proteasome upon purification. Despite the close phylogenetic relationship of piroplasmids and malaria, protocols to purify proteasome with measurable activity in assays with specific fluorescent peptidyl substrates has appeared challenging. Thus, our results could assist other researchers isolating proteasomes and cytoplasmic enzymes from more piroplasmid species.


P3

Generation of transgenic *Plasmodium falciparum* lines for functional characterization of genes putatively involved in sexual differentiation

M. Moser¹, K. Becker¹, K. Buchholz¹

¹Biochemistry and Molecular Biology, Justus Liebig University Giessen
E-mail: Melanie.Moser@ernaehrung.uni-giessen.de

Malaria continues to be a major burden on humanity. The estimated 219 million clinical cases and more than 435,000 deaths per year worldwide remain a key health problem. *Plasmodium falciparum* parasites have a complex life cycle, switching between a mammalian host and a mosquito vector. In the human body, massive amplification of asexual stages causes the pathology of the disease. During each of this replication cycles, a small subset of asexual parasites become committed to form sexual stages. These gametocytes circulate in the blood stream awaiting transmission to a mosquito vector. The developmental switch between asexual and sexual differentiation is of particular interest regarding the development of new antimalarial drugs. Counteracting the parasites’ sexual development suppresses the transmission, improves the morbidity and mortality of the disease and helps limiting the spread of resistance. The aim of this project is to validate and functionally characterize a variety of genes, which are hypothesized to be of importance for *Plasmodium* sexual differentiation. This is accomplished through generation of transgenic parasite lines and subsequent phenotypic characterization with a focus on sexual development. Here we will present preliminary data on the gametocyte development of selected knock down parasite lines. The genes of interest with an important phenotype for sexual differentiation will be further investigated, thus laying the basis for future innovative transmission-blocking therapeutic approaches.
Abstracts of Posters

P4
Exploring druggable hot spots in *Schistosoma mansoni* cathepsin B1 for structure-based design of vinyl sulfone inhibitors

A. Jilkova¹, P. Rubesova¹, J. Fanfrlik¹, P. Fajtova¹, P. Rezacova¹, J. Brynda¹, M. Lepsik¹, M. Horn¹, C. R. Caffrey², M. Mares¹

¹Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Flemingovo n. 2, Prague, 16610, Czech Republic; ²University of California San Diego, Center for Discovery and Innovation in Parasitic Diseases, Skaggs School of Pharmacy and Pharmaceutical Sciences, 9500 Gilman Drive, La Jolla, CA 92093, USA
E-mail: jilkova@uochb.cas.cz

Schistosomiasis, caused by parasitic blood flukes of the genus *Schistosoma*, afflicts over 240 million people worldwide. *Schistosoma mansoni* cathepsin B1 (SmCB1) is a gut-associated peptidase that digests host blood proteins and is a drug target for vinyl sulfone inhibitors. We present a detailed inhibition profiling of SmCB1 with a set of vinyl sulfone peptidomimetic derivatives. They were screened against recombinant SmCB1 and against *S. mansoni* schistosomula. This work provided two inhibitors of SmCB1 with the IC50 values in the sub-nanomolar range that are the most effective inhibitors of this enzyme reported to date. Their high resolution crystal structures in complex with SmCB1 were determined. Analysis of the inhibitor binding mode using quantum chemical calculations identified novel interaction hot spots that can be exploited for the rational design of anti-schistosomal chemotherapeutics.
Abstracts of Posters

P5

Schistosomes and snails in Côte d’Ivoire: hybrid schistosome infections and control

Yves-Nathan T. Tian-Bi1, Bonnie Webster2, Cyrille K. Konan1, Fiona Allan2, Nana R. Diakité1, Mamadou Ouattara1, Muriel Rabone2, Jean T. Coulibaly1, Stefanie Knopp3, Aboulaye Meïté4, Jürg Utzinger3, David Rollinson2 and Eliézer K. N’Goran1

1 Unité de Formation et de Recherche Biosciences, Université Félix Houphouët-Boigny, 22 BP 770, Abidjan 22, Côte d’Ivoire; 2 Wolfson Wellcome Biomedical Laboratories, Department of Life Sciences, Natural History Museum, Cromwell Road, London SW7 5BD, United Kingdom; 3 Swiss Tropical and Public Health Institute, P.O. Box, CH–4002 Basel, Switzerland; 4 Programme National de Lutte contre les Maladies Tropicales Négligées à Chimiothérapie Préventive (PNLMTN-CP), Ministère de la Santé et de l’Hygiène Publique, 06 BP 6394, Abidjan 06, Côte d’Ivoire

E mail: tianbyth@yahoo.fr

Hybrid schistosomes such as those involving Schistosoma haematobium (the agent of human urogenital schistosomiasis) and S. bovis (the agent of bovine intestinal schistosomiasis) constitute a public health concern in Africa [1]. In several African countries these schistosomes are transmitted by Bulinus snails. The occurrence of these hybrids in Côte d’Ivoire is also expected. Between June 2016 and March 2017, Bulinus spp. were sampled in human-water contact sites in northern and central Côte d’Ivoire. Molecular tools [2-3] were used to identify snails and determine S. haematobium group species and their interspecific hybrids infecting bulinid snails in a large part of the country. Only Bulinus truncatus and B. globosus snails were found infected with S. haematobium group species. Infection combinations involving S. bovis and hybrids were more prevalent in B. truncatus, whereas S. haematobium and hybrid infections were mainly seen in B. globosus. Our data provide the first evidence for the transmission of S. haematobium x S. bovis hybrids in Côte d’Ivoire and may indicate the occurrence of zoonotic transmission of schistosomes in the country. Due to their vigour, hybrid schistosomes might be involved in reduced efficacy of usual doses of praziquantel for schistosomiasis control [4]. This highlights the need for continued surveillance and the introduction of new control interventions.

Schistosomiasis is an infectious disease with zoonotic potential and caused by platyhelminths of the genus *Schistosoma*. This disease is endemic in Asia, South America and Africa. Infection occurs by contact with water through cercariae, a free-living larval stage of schistosomes, which penetrate the skin of their final host and develop into adult worms. Schistosomes are the only trematodes that live dioeciously. Following pairing, female worms start egg production. Via feces and urine, part of the eggs are released to the environment. The other part of eggs circulate via the blood stream to liver and spleen where they get trapped inside the tissues. As consequences, inflammatory processes are induced and liver fibrosis. There is no vaccine available yet, and only one drug that is effective against all schistosome species, Praziquantel (PZQ). Due to the fear of emerging resistance against PZQ, there is urgent need to find alternative treatment concepts. Goal of the presented work is characterizing genes whose expression products may represent potential target molecules for drug design. Among these target molecules are two aldehyde dehydrogenases (ALDHs), aldose reductase (AR), two Abl kinases (Abl1 and 2), and the Src/Abl hybrid tyrosine kinase 6 (TK6). Expression cloning of AR as well as one ALDH succeeded; first results will be presented.
Dithiocarbazate derivatives as potential anthelminthic agents against *schistosoma mansoni*

Gallinger, T. L.\(^1\), Rennar, G. A.\(^1\), Lange-Grünweller, K. C.\(^1\), Häberlein, S.\(^2\), Grünweller, A.\(^1\), Hartmann, R. K.\(^1\), Grevelding, C. G.\(^2\), Schlitzer, M.\(^1\)

\(^1\)Institut für Pharmazeutische Chemie, Philipps-Universität Marburg, Marbacher Weg 6-10, 35032 Marburg, \(^2\)Institut für Parasitologie, Justus-Liebig-Universität Gießen, Schubertstraße 81, 35392 Gießen

E-mail: tom.gallinger@pharmazie.uni-marburg.de

Schistosomiasis is one of the most important parasitic infections worldwide, and the treatment of the trematode-triggered disease is currently almost completely dependent on praziquantel. Due to the widespread and decades-long application, the concern about resistance development is great, so that there is a need for new antischistosomal substances [1-2].

In previous studies of our group, dithiocarbamates displayed antischistosomal activity, hence we also investigated the structurally related dithiocarbazates. After successful synthesis, the antischistosomal activity was examined through *in vitro* tests on adult *Schistosoma mansoni*. A number of initial derivatives exhibited activity against the parasites, providing another interesting starting point for the development of novel antischistosomal compounds. Subsequently, the toxicity of the active compounds to human cells was evaluated. A certain cytotoxicity was observed, thus this aspect will also be considered in future optimisations.

CTLA4-Ig – a potential drug for the treatment of hepatic fibrosis in schistosomiasis?

A. Rabes¹, M. Bischofsberger¹, F. Winkelmann¹, E. C. Reisinger¹, M. Sombetzki¹

¹Department of Tropical Medicine and Infectious Diseases. University Medical Center Rostock, Germany.
E-mail: anne.rabes@uni-rostock.de

Hepatic fibrosis and granuloma formation characterize the pathology of *Schistosoma mansoni* infection. We previously have shown that single-sex infection with female schistosomes mitigates hepatic fibrosis after secondary infection [1]. This was associated with an increased expression of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), known as a negative regulator of T cell activation. Based on these findings, we hypothesized that administration of agonistic CTLA4-Ig (belatacept) is capable to prevent and/or reverse hepatic fibrosis during schistosomiasis.

Mice were infected with 50 *S. mansoni* cercariae and 4 (early) or 8 (late) weeks post infection CTLA4-Ig or appropriated control-Ig were administered for 4 weeks. When given early in schistosomiasis, livers of CTLA4-Ig treated mice showed significantly reduced collagen deposition and decreased expression of pro-fibrotic genes in comparison to controls. In addition, administration of CTLA4-Ig suppressed the inflammatory T cell response in infected mice. However, if therapy was started later after eggs were deposited and fibrogenesis was already initiated, CTLA4-Ig had no impact on hepatic fibrosis.

In conclusion, we could demonstrate that CTLA-4 is an important regulator of *S. mansoni*-induced fibrosis by modulating T-cell responses. Our results show that early preventive, but not late, CTLA4-Ig treatment ameliorates liver fibrosis.

P9
Human serum differentially impacts membrane turnover of male and female *Schistosoma mansoni*

F. Winkelmann¹, A. Rabes¹, M. Bischofsberger¹, M. Frank², E. C. Reisinger¹, M. Sombetzki¹

¹Department of Tropical Medicine and Infectious Diseases. University Medical Center, Rostock, Germany; ²Medical Biology and Electron Microscopy Centre, Rostock University Medical Center, Rostock, Germany.
E-mail: franziska.winkelmann@med.uni-rostock.de

Adult worms of *Schistosoma mansoni* reside mated in the mesenteric veins. The female worm buries within the gynecophoric canal of its male partner and is closely surrounded by it. Therefore, the tegument of the male worm is the first point of attack of the human immune system. Previous work has focused on the immune evasion strategies of the males [1]. Due to its hidden position less is known about evasion strategies of female worms. We wanted to investigate whether the soluble part of the immune response differentially impacts male and female schistosomes.

Adult worms were separated by sex and incubated in normal human serum for different time points. Females out of a pair showed a marked reshaping of their membranocalyx after an incubation time of 30 minutes. This goes in lines with a significant increase of genes related to membrane turnover peaking at 24 hours of incubation. Male schistosomes start at earlier time points with tegument remodeling followed by a rapid normalization of gene expression levels. An effect on the motility or the viability of adult schistosomes was not detectable. These results indicate that female schistosomes evolved different evasion strategies towards the host's immune system in comparison to male schistosomes. This might impart a higher solidity and has to be taken into account for the development of new anti-schistosomal drugs.

Insects in anthelmintics discovery: lady beetle-derived harmonine as novel anti-parasitic “swiss army-knife”?

J. Kellershohn¹, L. Thomas², A. Grünweller², R. K. Hartmann², M. Hardt³, A. Vilcinskas⁴, C. G. Grevelding¹, S. Häberlein¹

¹Institute of Parasitology, BFS, Justus Liebig University Giessen, Germany; ²Institute of Pharmaceutical Chemistry, Philipps University, Marburg, Germany; ³Biomedical Research Center Seltersberg - Imaging Unit, Justus Liebig University Giessen, Germany; ⁴Institute for Insect Biotechnology, Justus Liebig University Giessen, Germany; Department Bioresources, Fraunhofer Institute for Molecular Biology and Applied Ecology (IME), Germany

E-mail: simone.haeberlein@vetmed.uni-giessen.de

Insects represent an innovative source for the discovery of novel antiparasitic compounds. Harmonine is an antimicrobial alkaloid of the harlequin ladybird Harmonia axyridis, and it showed a remarkable all-round activity against mycobacteria, Plasmodium and Leishmania [1-2]. To explore the anthelminthic potential of harmonine, we tested its effect on the blood fluke Schistosoma mansoni, and the common liver fluke Fasciola hepatica; both have zoonotic potential and affect millions of people and livestock worldwide.

Harmonine was lethal to adult S. mansoni at 10 µM in vitro. Motility was reduced to a minimum, female and male worms separated, and egg production was fully abolished even at 5 µM. Next to tegument blisters and prominent gut dilatations, structural disintegration of the reproductive organs was observed, including reduced sperm numbers and a significant reduction of proliferating gonadal stem cells. These findings point to a cellular target of harmonine involved in gonad development or function. In addition, acetylcholinesterase was revealed as one possible target, because harmonine partially inhibited the acetylcholine-hydrolyzing activity of schistosomal protein extracts [3]. Next to schistosomes, juvenile F. hepatica were killed by harmonine in vitro, in concentrations as low as 2.5 µM. To conclude, in addition to its antimicrobial and antiprotozoal effects, harmonine demonstrated anthelminthic activity. This study highlights the potential of exploiting insects as sources for the discovery of novel anthelminthic compounds.

Abl kinases as potential targets for candidate compounds in the liver fluke *Fasciola hepatica*

H. Houhou, C.G. Grevelding, S. Häberlein

Institute of Parasitology, BFS, Justus Liebig University Giessen, Germany
E-mail: simone.haeberlein@vetmed.uni-giessen.de

The liver fluke *Fasciola hepatica* is a trematode parasite and has zoonotic potential. It is a threat for both human and animal health, causing fasciolosis. This infectious disease produces enormous economic loss in cattle and sheep farming. Although triclabendazole is effective against *Fasciola*, several reports showed the spread of resistance against this drug. Therefore, finding alternative treatment options is highly demanded.

Protein-tyrosine kinases (PTKs) have gained interest as anti-parasitic targets [1]. We found promising effects of kinase inhibitors such as imatinib against the trematode *Schistosoma mansoni* [2]. Imatinib (Glivec, Novartis) is an Abl kinase inhibitor and an approved anti-cancer drug. Because of the highly conserved nature of Abl kinases, imatinib might be effective also against other platyhelminths such as *F. hepatica*.

To test this hypothesis we performed a genome-data search and found two Abl-kinase orthologues in *F. hepatica*. RT-qPCR analysis revealed their expression in all intramammalian stages: newly excysted juveniles (NEJs), 4-weeks old immature flukes, and 12-weeks old adults. Imatinib reduced motility of NEJs at 20 µM and was 100% lethal at 50 µM in vitro. In future work, we will test the efficacy against other stages. Furthermore, we aim to knock-down Abl kinase expression to confirm their role in *Fasciola* biology and to validate their suitability as potential drug target.


P12

P. falciparum pre-erythrocytic screening platform:
screening for causal prophylactics

J. M. Bolscher¹, Marie Miglianico¹, K. M. Koolen¹, Rianne van der Laak¹, Laura
Pelser-Posthumus¹,², Geert-Jan van Gemert², R. W. Sauerwein², A. Sturm¹,
K. J. Dechering¹

¹TropIQ Health Sciences, Nijmegen, The Netherlands, ²Radboud University Medical
Center, Nijmegen, The Netherlands

Email: a.sturm@tropiq.nl

To this day, still very little is known about the malaria pre-erythrocytic stages, the
developmental phases between sporozoite injection and liver-merozoite release. All of these
stages are clinically silent but are the only parasite forms that have been proven to induce
sterile immunity if stopped before entering the blood stage. Fortunately, recent years have
seen major improvements of the technical difficulties that have hindered research of the
human pre-erythrocytic stage for decades.

In order to accelerate drug discovery, we have established an in vitro, plate-based,
phenotypical screening cascade that allows us to identify compounds acting on viability,
gliding, traversal, and liver stage maturation of P. falciparum sporozoites.

Screening 70,000 compounds of the Global Health Diversity Library (GHDL) we found that
sporozoite viability is very difficult to interfere with. Nevertheless, we identified one potent
compound series with robust sporozoite killing activity, which also inhibits gliding as well as
invasion and maturation of P. falciparum liver stages. This compound series is now
undergoing hit to lead optimisation and has potential to provide the starting point for the
development of a new causal prophylaxis.
<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>Institution</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alunda</td>
<td>José Maria</td>
<td>Universidad Complutense de Madrid</td>
<td><a href="mailto:jmalunda@ucm.es">jmalunda@ucm.es</a></td>
</tr>
<tr>
<td>Angelova</td>
<td>Lora</td>
<td>MSD Animal Health Innovation GmbH</td>
<td><a href="mailto:lora-angelova@gmx.de">lora-angelova@gmx.de</a></td>
</tr>
<tr>
<td>Aucamp</td>
<td>Janine</td>
<td>JLU Gießen</td>
<td><a href="mailto:20505698@nwu.ac.za">20505698@nwu.ac.za</a></td>
</tr>
<tr>
<td>Becker</td>
<td>Katja</td>
<td>JLU Gießen</td>
<td><a href="mailto:katja.becker@uni-giessen.de">katja.becker@uni-giessen.de</a></td>
</tr>
<tr>
<td>Berneburg</td>
<td>Isabell</td>
<td>JLU Gießen</td>
<td><a href="mailto:isabell.berneburg@ernaehrung.uni-giessen.de">isabell.berneburg@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Beutler</td>
<td>Mandy</td>
<td>JLU Gießen</td>
<td><a href="mailto:Mandy.beutler@vetmed.uni-giessen.de">Mandy.beutler@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Bischofsberger</td>
<td>Miriam</td>
<td>Rostock University Medical Center</td>
<td><a href="mailto:miriam.bischofsberger@med.uni-rostock.de">miriam.bischofsberger@med.uni-rostock.de</a></td>
</tr>
<tr>
<td>Blume</td>
<td>Martin</td>
<td>Robert-Koch-Institut</td>
<td><a href="mailto:blumem@rki.de">blumem@rki.de</a></td>
</tr>
<tr>
<td>Brehm</td>
<td>Klaus</td>
<td>Julius-Maximilians-Universität Würzburg</td>
<td><a href="mailto:kbrehm@hygiene.uni-wuerzburg.de">kbrehm@hygiene.uni-wuerzburg.de</a></td>
</tr>
<tr>
<td>Buchholz</td>
<td>Kathrin</td>
<td>JLU Gießen</td>
<td><a href="mailto:kathrin.buchholz@ernaehrung.uni-giessen.de">kathrin.buchholz@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Caffrey</td>
<td>Conor</td>
<td>UC San Diego</td>
<td><a href="mailto:ccaffrey@ucsd.edu">ccaffrey@ucsd.edu</a></td>
</tr>
<tr>
<td>Chatterjee</td>
<td>Arnab</td>
<td>CALIBR</td>
<td><a href="mailto:achatterjee@calibr.org">achatterjee@calibr.org</a></td>
</tr>
<tr>
<td>Costi</td>
<td>Maria Paola</td>
<td>University of Modena and Reggio Emilia</td>
<td><a href="mailto:mariapaola.costi@unimore.it">mariapaola.costi@unimore.it</a></td>
</tr>
<tr>
<td>Dvorak</td>
<td>Jan</td>
<td>Czech University of Life Science Prague</td>
<td><a href="mailto:hdvorak76@outlook.com">hdvorak76@outlook.com</a></td>
</tr>
<tr>
<td>Falcone</td>
<td>Franco</td>
<td>University of Nottingham</td>
<td><a href="mailto:franco.falcone@nottingham.ac.uk">franco.falcone@nottingham.ac.uk</a></td>
</tr>
<tr>
<td>Gäsns</td>
<td>Daniela</td>
<td>JLU Gießen</td>
<td><a href="mailto:Daniela.Gaens@vetmed.uni-giessen.de">Daniela.Gaens@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Gallinger</td>
<td>Tom Lukas</td>
<td>Philipps-Universität Marburg</td>
<td><a href="mailto:Tom.gallinger@pharmazie.uni-marburg.de">Tom.gallinger@pharmazie.uni-marburg.de</a></td>
</tr>
<tr>
<td>Geyer</td>
<td>Joachim</td>
<td>JLU Gießen</td>
<td><a href="mailto:pharmtox@vetmed.uni-giessen.de">pharmtox@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Grevelding</td>
<td>Christoph</td>
<td>JLU Gießen</td>
<td><a href="mailto:Christoph.Grevelding@vetmed.uni-giessen.de">Christoph.Grevelding@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Grote-Gálvez</td>
<td>Rosa Isela</td>
<td>Bernhard-Nocht-Institut für Tropenmedizin</td>
<td><a href="mailto:Grote-galvez@bnitm.de">Grote-galvez@bnitm.de</a></td>
</tr>
<tr>
<td>Grünweller</td>
<td>Arnold</td>
<td>Philipps-Universität Marburg</td>
<td><a href="mailto:gruenwel@staff.uni-marburg.de">gruenwel@staff.uni-marburg.de</a></td>
</tr>
<tr>
<td>Last Name</td>
<td>First Name</td>
<td>Institution</td>
<td>E-mail</td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>--------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Haas</td>
<td>Helmut</td>
<td>helminGuard</td>
<td><a href="mailto:hhaas@helminguard.de">hhaas@helminguard.de</a></td>
</tr>
<tr>
<td>Häberlein</td>
<td>Simone</td>
<td>JLU Gießen</td>
<td><a href="mailto:Simone.hauberlein@vetmed.uni-giessen.de">Simone.hauberlein@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Hahnel</td>
<td>Steffen</td>
<td>Bayer Animal Health GmbH</td>
<td><a href="mailto:Reg_102558_Hahnel@semigator.de">Reg_102558_Hahnel@semigator.de</a></td>
</tr>
<tr>
<td>Harrington</td>
<td>John</td>
<td>Boehringer Ingelheim Animal Health</td>
<td><a href="mailto:john.harrington@boehringer-ingelheim.com">john.harrington@boehringer-ingelheim.com</a></td>
</tr>
<tr>
<td>Heimsch</td>
<td>Kim</td>
<td>JLU Gießen</td>
<td><a href="mailto:kim.heimsch@ernaehrung.uni-giessen.de">kim.heimsch@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Heisler</td>
<td>Iring</td>
<td>Bayer Animal Health</td>
<td><a href="mailto:reg_102558_heisler@semigator.de">reg_102558_heisler@semigator.de</a></td>
</tr>
<tr>
<td>Horn</td>
<td>Martin</td>
<td>Czech Academy of Sciences</td>
<td><a href="mailto:martin.horn@uochb.cas.cz">martin.horn@uochb.cas.cz</a></td>
</tr>
<tr>
<td>Houhou</td>
<td>Hicham</td>
<td>JLU Gießen</td>
<td><a href="mailto:Hicham.houhou@vetmed.uni-giessen.de">Hicham.houhou@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Jacobs</td>
<td>Thomas</td>
<td>Bernhard-Nocht-Institut für Tropenmedizin</td>
<td><a href="mailto:Tjacobs@bnitm.de">Tjacobs@bnitm.de</a></td>
</tr>
<tr>
<td>Janzen</td>
<td>Christian</td>
<td>Julius-Maximilians-Universität Würzburg</td>
<td><a href="mailto:christian.janzen@uni-wuerzburg.de">christian.janzen@uni-wuerzburg.de</a></td>
</tr>
<tr>
<td>Jilkova</td>
<td>Adela</td>
<td>Czech Academy of Sciences</td>
<td><a href="mailto:jilkova@uochb.cas.cz">jilkova@uochb.cas.cz</a></td>
</tr>
<tr>
<td>Kaiser</td>
<td>Annette</td>
<td>Universität Duisburg-Essen</td>
<td><a href="mailto:kaiser@microbiology-bonn.de">kaiser@microbiology-bonn.de</a></td>
</tr>
<tr>
<td>Kaminsky</td>
<td>Ronald</td>
<td>Para C. Consulting</td>
<td><a href="mailto:Para.c@gmx.de">Para.c@gmx.de</a></td>
</tr>
<tr>
<td>Karanis</td>
<td>Panagiotis</td>
<td>Universität zu Köln</td>
<td><a href="mailto:panagiotis.karanis@uk-koeln.de">panagiotis.karanis@uk-koeln.de</a></td>
</tr>
<tr>
<td>Koolman</td>
<td>Hannes</td>
<td>Boehringer Ingelheim</td>
<td><a href="mailto:hannes_fiepko.koolman@boehringer-ingelheim.com">hannes_fiepko.koolman@boehringer-ingelheim.com</a></td>
</tr>
<tr>
<td>Kopáček</td>
<td>Petr</td>
<td>Czech Academy of Sciences</td>
<td><a href="mailto:kopajz@paru.cas.cz">kopajz@paru.cas.cz</a></td>
</tr>
<tr>
<td>Kraus</td>
<td>Amelie</td>
<td>LMU München</td>
<td><a href="mailto:Amelie.kraus@lmu.de">Amelie.kraus@lmu.de</a></td>
</tr>
<tr>
<td>Lespine</td>
<td>Anne</td>
<td>INRA</td>
<td><a href="mailto:Anne.lespine@inra.fr">Anne.lespine@inra.fr</a></td>
</tr>
<tr>
<td>Leurs</td>
<td>Rob</td>
<td>Vrije Universiteit Amsterdam</td>
<td><a href="mailto:r.leurs@vu.nl">r.leurs@vu.nl</a></td>
</tr>
<tr>
<td>Long</td>
<td>Alan</td>
<td>Boehringer Ingelheim Animal Health</td>
<td><a href="mailto:al.long@boehringer-ingelheim.com">al.long@boehringer-ingelheim.com</a></td>
</tr>
<tr>
<td>Lundström-Stadelmann</td>
<td>Britta</td>
<td>Universität Bern – Vetsuisse</td>
<td><a href="mailto:britta.lundstroem@vetsuisse.unibe.ch">britta.lundstroem@vetsuisse.unibe.ch</a></td>
</tr>
</tbody>
</table>
## List of Participants

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>Institution</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin</td>
<td>Julio</td>
<td>GlaxoSmithKline</td>
<td><a href="mailto:julio.j.martin@gsk.com">julio.j.martin@gsk.com</a></td>
</tr>
<tr>
<td>Maule</td>
<td>Aaron</td>
<td>Queen’s University Belfast</td>
<td><a href="mailto:A.Maule@qub.ac.uk">A.Maule@qub.ac.uk</a></td>
</tr>
<tr>
<td>Moser</td>
<td>Melanie</td>
<td>JLU Gießen</td>
<td><a href="mailto:melanie.moser@ernaehrung.uni-giessen.de">melanie.moser@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Mughal</td>
<td>Mudassar</td>
<td>JLU Gießen</td>
<td><a href="mailto:mudassar.n.mughal@vetmed.uni-giessen.de">mudassar.n.mughal@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Müller</td>
<td>Christin</td>
<td>JLU Gießen</td>
<td><a href="mailto:christin.mueller@viro.med.uni-giessen.de">christin.mueller@viro.med.uni-giessen.de</a></td>
</tr>
<tr>
<td>Müller</td>
<td>Joachim</td>
<td>Universität Bern</td>
<td><a href="mailto:joachim.mueller@vetsuisse.unibe.ch">joachim.mueller@vetsuisse.unibe.ch</a></td>
</tr>
<tr>
<td>Müller</td>
<td>Laura</td>
<td>LMU München</td>
<td><a href="mailto:laura.mueller-huebner@para.vetmed.uni-muenchen.de">laura.mueller-huebner@para.vetmed.uni-muenchen.de</a></td>
</tr>
<tr>
<td>Müller</td>
<td>Simon Franz</td>
<td>JLU Gießen</td>
<td><a href="mailto:simon.mueller@vetmed.uni-giessen.de">simon.mueller@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Noack</td>
<td>Sandra</td>
<td>Boehringer Ingelheim Vetmedica GmbH</td>
<td><a href="mailto:sandra.noack@boehringer-ingelheim.com">sandra.noack@boehringer-ingelheim.com</a></td>
</tr>
<tr>
<td>Olias-Molero</td>
<td>Ana Isabel</td>
<td>Universidad Complutense de Madrid</td>
<td><a href="mailto:anaolias@ucm.es">anaolias@ucm.es</a></td>
</tr>
<tr>
<td>Perner</td>
<td>Jan</td>
<td>Czech Academy of Sciences</td>
<td><a href="mailto:perner@paru.cas.cz">perner@paru.cas.cz</a></td>
</tr>
<tr>
<td>Peter Ventura</td>
<td>Alejandra</td>
<td>Philipps-Universität Marburg</td>
<td><a href="mailto:peterven@staff.uni-marburg.de">peterven@staff.uni-marburg.de</a></td>
</tr>
<tr>
<td>Pauli</td>
<td>Kathrin</td>
<td>JLU Gießen</td>
<td><a href="mailto:kathrin.pauli@ernaehrung.uni-giessen.de">kathrin.pauli@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Quack</td>
<td>Thomas</td>
<td>JLU Gießen</td>
<td><a href="mailto:thomas.quack@vetmed.uni-giessen.de">thomas.quack@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Rabes</td>
<td>Anne</td>
<td>Universität Rostock</td>
<td><a href="mailto:anne.rabes@uni-rostock.de">anne.rabes@uni-rostock.de</a></td>
</tr>
<tr>
<td>Rahlfis</td>
<td>Stefan</td>
<td>JLU Gießen</td>
<td><a href="mailto:stefan.rahlfis@ernaehrung.uni-giessen.de">stefan.rahlfis@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Rennar</td>
<td>Georg</td>
<td>Philipps-Universität Marburg</td>
<td><a href="mailto:georg.rennar@pharmazie.uni-marburg.de">georg.rennar@pharmazie.uni-marburg.de</a></td>
</tr>
<tr>
<td>Robbertse</td>
<td>Luise</td>
<td>Czech Academy of Sciences</td>
<td><a href="mailto:luise.robbertse@paru.cas.cz">luise.robbertse@paru.cas.cz</a></td>
</tr>
<tr>
<td>Rufener</td>
<td>Reto</td>
<td>Universität Bern</td>
<td><a href="mailto:reto.rufener@vetsuisse.unibe.ch">reto.rufener@vetsuisse.unibe.ch</a></td>
</tr>
<tr>
<td>Sager</td>
<td>Heinz</td>
<td>Elanco Tiergesundheit AG</td>
<td><a href="mailto:heinz.sager@elanco.com">heinz.sager@elanco.com</a></td>
</tr>
<tr>
<td>Schneider</td>
<td>Carolin</td>
<td>MSD Animal Health Innovation GmbH</td>
<td><a href="mailto:carolin.schneider@msd.de">carolin.schneider@msd.de</a></td>
</tr>
<tr>
<td>Last Name</td>
<td>First Name</td>
<td>Institution</td>
<td>E-mail</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
<td>-------------</td>
<td>--------</td>
</tr>
<tr>
<td>Schlitzer</td>
<td>Martin</td>
<td>Philipps-Universität Marburg</td>
<td><a href="mailto:schlitzer@staff.uni-marburg.de">schlitzer@staff.uni-marburg.de</a></td>
</tr>
<tr>
<td>Schuh</td>
<td>Katharina</td>
<td>JLU Gießen</td>
<td><a href="mailto:katharina.schuh@ernaehrung.uni-giessen.de">katharina.schuh@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Schulz</td>
<td>Cindy</td>
<td>Universität Rostock</td>
<td><a href="mailto:cindy.schulz@uni-rostock.de">cindy.schulz@uni-rostock.de</a></td>
</tr>
<tr>
<td>Sekljic</td>
<td>Harald</td>
<td>MSD Animal Health Innovation GmbH</td>
<td><a href="mailto:harald.sekljic@msd.de">harald.sekljic@msd.de</a></td>
</tr>
<tr>
<td>Selzer</td>
<td>Paul</td>
<td>Boehringer Ingelheim Vetmedica GmbH</td>
<td><a href="mailto:paul.selzer@boehringer-ingelheim.com">paul.selzer@boehringer-ingelheim.com</a></td>
</tr>
<tr>
<td>Silva</td>
<td>Liliana</td>
<td>JLU Gießen</td>
<td><a href="mailto:Liliana.silva@vetmed.uni-giessen.de">Liliana.silva@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Siegl</td>
<td>Nicolai</td>
<td>LMU München</td>
<td><a href="mailto:n.sieg@lmu.de">n.sieg@lmu.de</a></td>
</tr>
<tr>
<td>Sojka</td>
<td>Daniel</td>
<td>Biology Centre of the Czech Academy of Sciences</td>
<td><a href="mailto:sojkadan@gmail.com">sojkadan@gmail.com</a></td>
</tr>
<tr>
<td>Soldati-Favre</td>
<td>Dominique</td>
<td>Universität Genf</td>
<td><a href="mailto:dominique.soldati-favre@unige.ch">dominique.soldati-favre@unige.ch</a></td>
</tr>
<tr>
<td>Sombetzki</td>
<td>Martina</td>
<td>Universität Rostock</td>
<td><a href="mailto:martina.sombetzki@uni-rostock.de">martina.sombetzki@uni-rostock.de</a></td>
</tr>
<tr>
<td>Springer</td>
<td>Eric</td>
<td>JLU Gießen</td>
<td><a href="mailto:eric.springer@ernaehrung.uni-giessen.de">eric.springer@ernaehrung.uni-giessen.de</a></td>
</tr>
<tr>
<td>Sterk</td>
<td>Geert</td>
<td>VU University Amsterdam</td>
<td><a href="mailto:g.j.sterk@vu.nl">g.j.sterk@vu.nl</a></td>
</tr>
<tr>
<td>Sturm</td>
<td>Angelika</td>
<td>TropiQ Health Sciences</td>
<td><a href="mailto:a.sturm@gmail.com">a.sturm@gmail.com</a></td>
</tr>
<tr>
<td>Taubert</td>
<td>Anja</td>
<td>JLU Gießen</td>
<td><a href="mailto:Anja.taubert@vetmed.uni-giessen.de">Anja.taubert@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Tian-Bi</td>
<td>Yves-Nathan</td>
<td>Université Félix Houphouet-Bogny / z.Zt. JLU</td>
<td><a href="mailto:tianbyth@yahoo.fr">tianbyth@yahoo.fr</a></td>
</tr>
<tr>
<td>Tonk</td>
<td>Miray</td>
<td>JLU Gießen</td>
<td><a href="mailto:miray.tonk@agrari.uni-giessen.de">miray.tonk@agrari.uni-giessen.de</a></td>
</tr>
<tr>
<td>Velez</td>
<td>Juan</td>
<td>JLU Gießen</td>
<td><a href="mailto:juan.velez@vetmed.uni-giessen.de">juan.velez@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Veijzagic</td>
<td>Nermina</td>
<td>TU München</td>
<td><a href="mailto:nermina.veijzagic@tum.de">nermina.veijzagic@tum.de</a></td>
</tr>
<tr>
<td>Villagra-Blanco</td>
<td>Rodolfo</td>
<td>JLU Gießen</td>
<td><a href="mailto:lora-angelova@gmx.de">lora-angelova@gmx.de</a></td>
</tr>
<tr>
<td>Vilcinskas</td>
<td>Andreas</td>
<td>JLU Gießen</td>
<td><a href="mailto:andreas.vilcinskas@agrari.uni-giessen.de">andreas.vilcinskas@agrari.uni-giessen.de</a></td>
</tr>
<tr>
<td>Vock</td>
<td>Carsten</td>
<td>Universität Wien</td>
<td><a href="mailto:carsten.vock@univie.ac.at">carsten.vock@univie.ac.at</a></td>
</tr>
<tr>
<td>Last Name</td>
<td>First Name</td>
<td>Institution</td>
<td>E-mail</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------</td>
<td>---------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>von Samson-Himmelstjerna</td>
<td>Georg</td>
<td>Freie Universität Berlin</td>
<td><a href="mailto:gvsamson@fu-berlin.de">gvsamson@fu-berlin.de</a></td>
</tr>
<tr>
<td>Weth</td>
<td>Oliver</td>
<td>JLU Gießen</td>
<td><a href="mailto:oliver.weth@vetmed.uni-giessen.de">oliver.weth@vetmed.uni-giessen.de</a></td>
</tr>
<tr>
<td>Winkelmann</td>
<td>Franziska</td>
<td>Universität Rostock</td>
<td><a href="mailto:franziska.winkelmann@med.uni-rostock.de">franziska.winkelmann@med.uni-rostock.de</a></td>
</tr>
<tr>
<td>Zheng</td>
<td>Yang</td>
<td>VU Amsterdam</td>
<td><a href="mailto:y.z.zheng@vu.nl">y.z.zheng@vu.nl</a></td>
</tr>
<tr>
<td>Zurbriggen</td>
<td>Raphael</td>
<td>Universität Bern</td>
<td><a href="mailto:raphael.zurbriggen@vetsuisse.unibe.ch">raphael.zurbriggen@vetsuisse.unibe.ch</a></td>
</tr>
</tbody>
</table>
We would like to thank the sponsors of the 20th Drug Design & Development Seminar of the German Society for Parasitology (DGP) & the LOEWE Center DRUID for their support:

**Boehringer Ingelheim Vetmedica GmbH**  
Binger Straße 173  
55216 Ingelheim am Rhein  
Germany  
[www.boehringer-ingelheim.de](http://www.boehringer-ingelheim.de)

**Jung-Stiftung für Wissenschaft und Forschung**  
Elbchaussee 215  
22605 Hamburg  
Germany  
[www.jung-stiftung.de](http://www.jung-stiftung.de)

**Merck KGaA**  
Frankfurter Straße 250  
64293 Darmstadt  
Germany  
[www.merck.de](http://www.merck.de)

**EUROIMMUN AG**  
Seekamp 31  
23560 Lübeck  
Germany  
[www.euroimmun.de](http://www.euroimmun.de)

**SANOFI**  
Sanofi-Aventis Deutschland GmbH  
Industriepark Höchst, K703  
65926 Frankfurt  
[www.sanofi.de](http://www.sanofi.de)

**TransMIT GmbH**  
Kerkrader Straße 3  
35394 Gießen  
[www.transmit.de](http://www.transmit.de)
Looking for the right resources?
Update your library today

20% Discount
Order via wiley.com using promotion code VBR13*

Comprehensive Analysis of Parasite Biology
From Metabolism to Drug Discovery
Sylke Müller (Editor),
Rachel Cerdan (Editor),
Ovidiu Radulescu (Editor),
Paul M. Selzer (Series Editor)
ISBN: 978-3-527-33904-4
576 pages • October 2016

Host - Pathogen Interaction
Microbial Metabolism, Pathogenicity and Antiinfectives
Gottfried Uden (Editor),
Eckhard Thines (Editor),
Anja Schufler (Editor),
Paul M. Selzer (Series Editor)
ISBN: 978-3-527-33745-3
240 pages • September 2016

Trypanosomatid Diseases
Molecular Routes to Drug Discovery
Timo Jager (Editor),
Oliver Koch (Editor),
Leopold Flohe (Editor),
Paul M. Selzer (Series Editor)
ISBN: 978-3-527-33255-7
576 pages • May 2013

Protein Phosphorylation in Parasites
Novel Targets for Antiparasitic Intervention
Christian Doerig (Editor),
Gerald Spaeth (Editor),
Martin Wiese (Editor),
Paul M. Selzer (Series Editor)
ISBN: 978-3-527-33235-9
456 pages • January 2014

Ectoparasites
Drug Discovery Against Moving Targets
Charles Q. Meng (Editor),
Ann E. Sluder (Editor),
Paul M. Selzer (Series Editor)
ISBN: 978-3-527-34168-9
376 pages • July 2018

ALSO AVAILABLE ONLINE

For more information on how Wiley can help you build your skills, visit our Professional Sciences Resource page.
www.wiley.com/learn/professionalscience

*Promotion code valid until December 31, 2019