Deutsche Gesellschaft für Parasitologie

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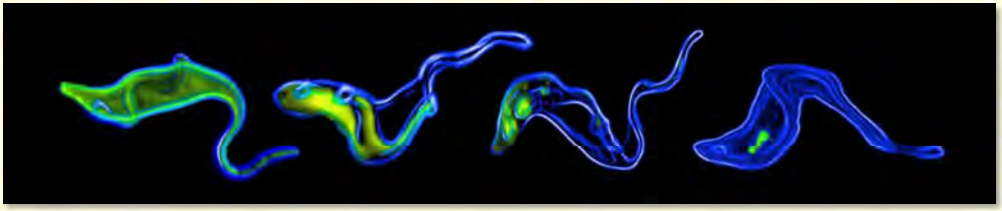
24th Drug Design & Development Seminar (DDDS)

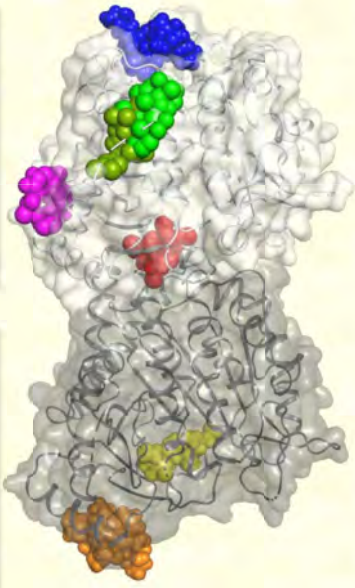
of the German Society for Parasitology (DGP)

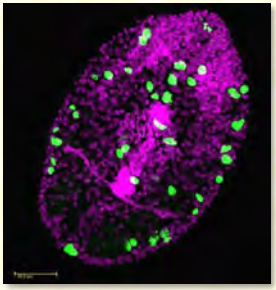
Combining Efforts towards Human and Animal Parasitic Diseases

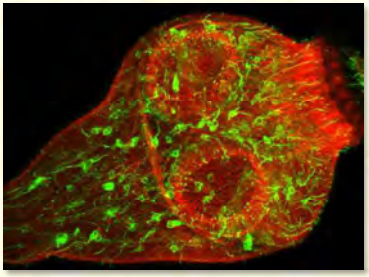
March 12th – 15th, 2024

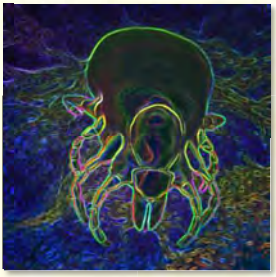
Würzburg, Germany











Cover legend

Top:

Trypanosomes (blue) internalizing anti-trypanosome antibodies (green) (© Markus Engstler, University of Würzburg, Germany)

Left middle and bottom:

Tsetse fly feeding on artificial human skin (© Markus Engstler, University of Würzburg, Germany); *Echinococcus* (© Klaus Brehm, University of Würzburg, Germany)

Right middle and bottom:

Fluke *Fasciola hepatica* (© Aaron Maule, Queen's University Belfast, UK); *Ixodes* tick artistic picture (© Boehringer Ingelheim, Germany)

Middle:

Tetrahymena thermophila tubulin structure highlighting the six distinct drug-binding sites found in mammalian tubulin. Adopted from Gaillard N et al., EMBO Mol Med. 2021 Nov 8;13(11):e13818. doi: 10.15252/emmm.202013818. (courtesy of Natcha Gaillard and Ashwani Sharma, ASTRA Therapeutics, Villigen, Switzerland)

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German Society for Parasitology & Ludwig-Maximilians University Würzburg

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 (Univ. of Zürich, CH), Prof. Dr. Rolf Walter (BNI, Hamburg, DE), and Prof. Dr. Heiner Schirmer (Univ. of Heidelberg, DE). Since 2004 Prof. Dr. Paul M. Selzer (Boehringer Ingelheim Animal Health, Ingelheim, DE) is the 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 aim and stimulate One-Health approaches to combat parasitic diseases. The main topics include but are not limited to:

- Target identification, characterization, and validation
- Identification of modulators
- Synthesis and optimization of lead compounds towards marketable drugs
- Testing active compounds in animal models

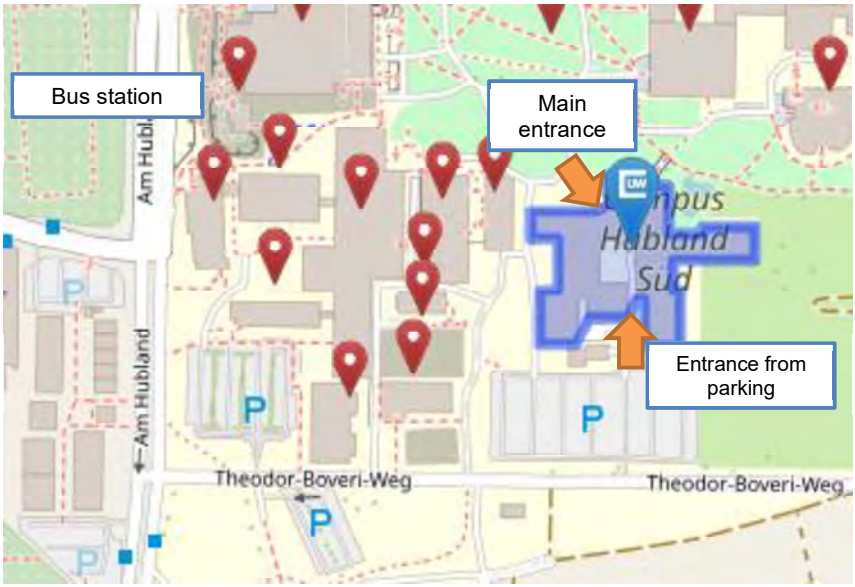
Venue

The Biocenter of the University of Würzburg

Am Hubland, 97074 Würzburg, Germany

The conference venue can be easily reached by public transportation, taking bus lines 114 or 214 from the city center to Hubland/Mensa bus station (lines 14 and 29 are also possible but are less convenient).

If you plan to come by car, please navigate to "Theodor-Boveri-Weg", where parking is available.
Link Google maps



The conference Dinner will take place at the Bürgerspital Weinstuben Restaurant right in the center of Würzburg, Theater Strasse 19, 97070 Würzburg Bürgerspital Restaurant Würzburg (buergerspital-weinstuben.de), which can be easily reached by bus line 114.

Collaboration Driving Innovation in Animal Health

Partnering in Parasitology

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Our goal is to discover and develop breakthroughs in animal health for diseases with significant unmet need. To achieve this we're investing in cutting-edge science and technology to expand and accelerate our drug discovery for the next generation of treatments and preventive therapies. We are a longstanding leader in parasitology, and a global innovator of highly-regarded anti-parasitic treatments, many of which are anchored in external innovation. In addition, we continue to pursue first-in-class innovation across a range of parasitic diseases where limited or no treatment options exist.

Collaborations with innovative and entrepreneurial partners are helping solve the biggest challenges in animal health. We believe that by working together we can bring critical diversity to innovation and accelerate the next wave of therapeutics that will transform the health and well-being of animals now and in generations to come.

Partnering Interests

Actively pursuing new partnerships in our research focus areas and open to a variety of partnership models to explore:

- Sustainable development / Green Chemistry technologies
- Prevention of canine heartworm disease
- Treatment of GI nematodes in pets and livestock
- Ectoparasites in all host species
- Coccidia in poultry and ruminants
- Fluke in ruminants.

Research Focus

- Solutions for a variety of species with an emphasis on: Endoparasites, Prevention/treatment of vector-born diseases (ectoparasites), Improved prevention/ treatment of coccidia.
- Opportunities to build on established brands with novel formulations and combination approaches.

Scan Me

Collaboration Driving Innovation

- Growing our global community of innovation partners
- Multiple collaborations advancing new therapies
- Long-term partnerships for the next generation of breakthroughs

Investing in Innovation

>€450 million
R&D for new medicines

Global
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>250
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Contact

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Life forward

Date of preparation: January 2024

Tuesday, 12.03.2024		
17:30	**20:00**	**Registration - The Biocenter of the University of Würzburg**
18:00	**20:00**	**Welcome Reception - The Biocenter of the University of Würzburg**

Wednesday, 13.03.2024			Speaker	Title	Institution
8:00	**9:00**	**Registration & Poster set-up**			
9:00	**9:20**	**Welcome & Introduction**	**Markus Engstler, Klaus Brehm, Paul M. Selzer, Sandra Noack**		
9:20	**10:00**	Keynote	Petr Volf	Sand fly-*Leishmania* interaction: different mechanisms of parasite attachment to the sand fly midgut	Charles University, Prague Praha, Czech Republic
10:00	**10:20**	Session Chair: Koen Dechering	Marnix Vlot	Unlocking cutting-edge technologies in antiparasitics discovery for small R&D labs	TropIQ Health Sciences, The Netherlands
10:20	**10:40**		Anette Kaiser	The hypusine pathway in *Ixodes rizinus*: Cloning and characterization of deoxyhypusine synthase as a novel target for drug discovery to treat and prevent vector borne diseases	Medical Research Centre, University of Bonn, Germany
10:40	**11:10**	**Coffee break**			
11:10	**11:50**	Keynote	Mike Barrett	New drugs for the African Animal Trypanosomiases	University of Glasgow, UK
11:50	**12:10**	Session Chair: Steffen Hahnel	Susanne Kramer	The mRNA decapping enzyme of *Trypanosoma brucei* is a promising drug target	University of Würzburg, Germany
12:10	**12:30**		Eric Schwegler	Inhibitor fluorination fine-tunes inactivation and induced dimerization of essential oxidoreductases from pathogenic trypanosomatids	Friedrich-Schiller University Jena, Germany
12:30	**12:50**		Tom Beneke	Co-expression of a cytosine base editor, a T7 RNA Polymerase and a Cas12a nuclease variant enables functional screens in *Leishmania* species	University of Würzburg, Germany
12:50	**13:00**	**Group picture of participants**			
13:00	**14:10**	**Lunch break**			

Wednesday, 13.03.2024			Speaker	Title	Institution
14:10	**14:50**	Keynote	Roger Prichard	Heartworm Disease: Drug resistance and the search for new preventives	McGill University, Montreal, Canada
14:50	**15:10**	Session Chair: Anne Lespine	Sara Lustigman	Repurposed drugs that target various stages of filarial worms can support the elimination goals for onchocerciasis	New York Blood Center, USA
15:10	**15:30**		Leonidas Spathis	Transcriptomic analysis unveils potential novel control targets for filarial nematode infections	University of Glasgow, Scotland, UK
15:30	**15:50**		Makedonka Mitreva	Pan-Nematoda potential of small molecule inhibitors of PIM kinases as new class of oral anthelmintics	Washington University, USA
15:50	**16:20**	**Coffee break**			
16:20	**16:40**	Session Chair: Pierre Gatel	Claude Charvet	Action of 5-aminovalerate on GABA-gated channels from chicken and its parasite *Ascaridia galli*	INRAE, Université de Tours, France
16:40	**17:00**		Hala Fahs	Multi-species nematode screening uncovers new classes of broad-spectrum anthelmintic compounds	New York University, USA
17:00	**17:20**		Geng Pan	Exploring the antiparasitic effects and active compounds of bio-refined Trifolium pratense (Red Clover)	University of Copenhagen, Denmark
17:20	**19:00**	**Poster session**			

Thursday, 14.03.2024			Speaker	Title	Institution
9:00	**9:40**	Keynote	Stephen R. Doyle	Genomic insights into drug response by helminths that infect animals and humans	Wellcome Sanger Institute, Hinxton, Cambridge, UK
9:40	**10:00**	Session Chair: Susanne Kramer	Lucas Barat	Comparative transcriptomic analysis in the *Caenorhabditis elegans* parasite model: impact of NHR-8	INRAE Toulouse, France
10:00	**10:20**		Maria Paola Costi	Leveraging proteomics, bioinformatics, and ecotoxicology models to select new targets overcoming *L. infantum* drug resistance	University of Modena and Reggio Emilia, Italy
10:20	**10:40**		Thomas Spangenberg	Assessing the propensity of selecting mutant parasites for the antimalarial drug cabamiquine	Global Health Institute of Merck, Ares Trading SA, Switzerland
10:40	**11:10**	**Coffee break**			
11:10	**11:50**	Keynote	Raffi Aroian	A novel approach to control intestinal parasites - "Fermented anthelmintics"	University of Massachusetts Chan Medical School, Worcester, USA
11:50	**12:10**	Session Chair: Christoph Grevelding	Jonathan Marchant	The tortoise and the hare: a characterization of two schistosome TRPM ion channels	Medical College of Wisconsin, USA
12:10	**12:30**		Elizabeth Holmes	Stuck in a toxic relationship: hERG and cytotoxicity mitigation in schistosomiasis drug discovery	Drug Discovery Unit, University of Dundee, UK
12:30	**12:50**		Bernardo Moreira	Targeting of *Schistosoma mansoni* c-Jun N-terminal kinase JNK by type II-kinase inhibitors with potent antischistosomal activity	Justus-Liebig-Universität Gießen, Germany
12:50		**Group picture of participants**			
12:50	**14:10**	**Lunch break**			
14:10	**14:50**	Keynote	Jennifer Keiser	Recent progress in the treatment of soil-transmitted helminthiasis	Swiss Tropical and Public Health Institute, Switzerland
14:50	**15:10**	Session Chair: Aaron Maule	Max Bär	Genetic makeup of a *Trichuris* species, not responding to drug treatment in Côte d'Ivoire and potential drug targets from comparative genomic analyses	Swiss Tropical and Public Health Institute, Switzerland
15:10	**15:30**		Youssef Hamway	Identification of a novel, multi-stage anti-schistosomal derived from mouse serum	Technical University Munich, Germany

15:30	**15:50**		Felix Mühlemeyer	Anthelmintic natural product discovery using *C. elegans* and *S. mansoni* screenings	Justus-Liebig-Universität Gießen, Germany
15:50	**16:20**	**Coffee break**			
16:20	**16:40**	Session Chair: Claude Charvet	Mohamed Issouf	Characterization of anthelminthic properties of plants from Mayotte island	MayBiotech, Mayotte Island, France
16:40	**17:00**		Emily Robb	Serotonergic signalling modulates movement and growth in juvenile liver fluke, *Fasciola hepatica*	Queen's University Belfast, UK
17:00	**17:20**		Rebecca Armstrong	Triggering apoptosis in juvenile liver fluke – a novel strategy for control?	Queen's University Belfast, UK
		Transfer on one's own to conference dinner			
19:00	**22:00**	**Conference Dinner - Bürgerspital Weinstuben**			

Friday, 15.03.2024			Speaker	Title	Institution
9:00	**9:40**	Keynote	Simone Häberlein	FasciolOmics - Omics-driven discovery of drugs and drug targets against liver flukes	Justus-Liebig-Universität Gießen, Germany
9:40	**10:00**	Session Chair: Britta Lundström-Stadelmann	Elena Ciccone	Application of RNA Technologies for improved control of cystic echinococcosis	University of Naples, Italy
10:00	**10:20**		Marc Kaethner	Investigation of the threonine metabolism of *Echinococcus multilocularis*: EmTDH as a potential drug target against alveolar echinococcosis	University of Bern, Switzerland
10:20	**10:40**		Daniel Sprague	Target-based design of metabolically stable cestocides	Medical College of Wisconsin, USA
10:40	**11:10**	**Coffee break**			
11:10	**11:50**	Keynote	Natcha Gaillard & Ashwani Sharma	Precision designed anti-pathogen drugs	ASTRA Therapeutics, Villigen, Switzerland
11:50	**12:10**	Session Chair: Richard Marhöfer	Kai Hänggeli	Evaluation of the trithiolato-bridged arene ruthenium complex conjugated to 9-(2-hydroxylethyl)-adenine (OD62-18) as a potential treatment for *Toxoplasma gondii* infection	University of Bern, Switzerland
12:10	**12:30**		Tobias Kämpfer	Assessment of triclabendazole treatment against *E. multilocularis*	University of Bern, Switzerland
12:30	**12:50**		Sara Benazzouz	In vitro drug screening cascade for *Echinococcus granulosus*	University of Bern, Switzerland
12:50	**13:00**	**Wrap-up & Closing**	**Paul M. Selzer**		

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Poster	Name	Title	Institution
P1	Frederic Risch	Pre-clinical development of corallopyronin A – update on pharmacology and validation of an amorphous solid dispersion formulation	University Hospital Bonn, Germany
P2	Leticia Pereira	Substrate specificity of the unique trypanosome mRNA decapping enzyme	University of Würzburg, Germany; Carlos Chagas Institute (ICC), FIOCRUZ/PR, Curitiba, Brazil
P3	Sophie Welsch	Analysis of the antipathogenic potential of rocaglates and their targets in *Schistosoma mansoni*	Justus Liebig University Gießen, Germany
P4	Maria Gorna	Structure-function studies of the mRNA decapping enzyme of *Trypanosoma brucei*	Charles University in Prague, BIOCEV, Prague, Czech Republic
P5	Pascal Zumstein	Investigation of the malate dismutation pathway as a potential drug target in *Echinococcus multilocularis*	University of Bern, Switzerland
P6	Anissa Bartetzko	Response to alveolar echinococcosis: Screening of the MMV Pandemic Response Box revealed a novel promising compound	University of Bern, Switzerland
P7	Maria Grechnikova	Targeting a unique mRNA decapping enzyme for trypanosomatid infectious disease drug discovery	Charles University in Prague, BIOCEV, Prague, Czech Republic
P8	Maria Cristina Ferreira de Sousa	Activity and efficacy of the bumped kinase inhibitor BKI-1708 in vitro and in non-pregnant and pregnant toxoplasmosis and neosporosis mouse models	University of Bern, Switzerland
P9	Matías Preza	Niclosamide ethanolamine against the fox tapeworm, *Echinococcus multilocularis*	University of Bern, Switzerland
P10	Josephine Forde-Thomas	Identification of anti-schistosomal starting points within Merck KGaA's Open Innovation Initiatives	Aberystwyth University, UK
P11	Natalie Wiedemar	Tools for investigation of drug resistance and screening of new compounds in the liver fluke *Fasciola hepatica*	University of Bern, Switzerland
P12	David Moody	Glycolysis is not a suitable pathway for identifying anthelmintic targets in *C. elegans* under standard growth conditions	University of Glasgow, Glasgow, UK
P13	Ali Raza	How do seaweed bioactive compounds kill parasitic worms?	University of Copenhagen, Denmark
P14	Luisa Schiegl	Hippo and *Echinococcus* growth control	University of Würzburg, Germany
P15	Jil Roßberg	Establishing state-of-the-art infrastructure for arthropod repellent discovery	IS Insect Services GmbH, Berlin, Germany

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Sand fly-Leishmania interaction: different mechanisms of parasite attachment to the sand fly midgut

Petr Volf

Department of Parasitology, Faculty of Science, Charles University, Prague, Czech Republic

E-mail: volf@cesnet.cz

In digestive tract of the sand fly vector *Leishmania* undergo morphological changes, transforming from amastigotes to promastigotes and creating various promastigote forms. The critical steps in this part of the life cycle include development inside the bloodmeal surrounded by the peritrophic matrix, attachment to the sand fly midgut epithelium, anterior migration and attachment to the stomodeal valve. Each step is facilitated by specific molecules.

Nectomonads and leptomonads, parasite forms found in the middle phase of development in sand fly, bind to midgut epithelium by inserting flagella between microvilli [1]. The binding mechanism differs between sand fly species. In *P. papatasi*, the specific vector, the attachment to microvilli is controlled by galectin which serves as a receptor for terminal galactose present on *L. major* lipophosphoglycan (LPG) [2]. In contrast, in permissive sand flies the attachment does not require LPG and is mediated by sand fly O-linked glycoproteins detected in midgut of permissive species [3,4]. In *Lutzomyia longipalpis* this glycoprotein was characterized as a novel mucin localized on midgut microvilli [5].

Specialized haptomonad forms attach to cuticular lining of the stomodeal valve and destroy its cells [6], enabling the parasite transmission by regurgitation. The flagellum of haptomonads is modified to the attachment plaque which contains distinct structural elements and specific proteins [7]. *Leishmania mexicana* knockouts mutated in these kinetoplastid-insect attachment proteins (KIAPS) develop vigorously in the sand fly midgut but they are not able to attach to the stomodeal valve [8].

[1] Wilson R. et al, 2010. PLoS NTD 4: e 816.
[2] Kamhawi S. et al., 2004. Cell 119: 329-341.
[3] Volf P. and Myskova J., 2007. Trends Parasitol. 23: 91-92.
[4] Svarovska A. et al., 2010. PLoS NTD 4: e580.
[5] Myskova J. et al., 2016. Parasites and Vectors 9: 413.
[6] Volf P. et al,. 2004. Int. J. Parasitol. 34: 1221-1227.
[7] Yanase R. et al., 2023. eLife 12: e84552
[8] Yanase R. et al., unpublished.

Unlocking cutting-edge technologies in antiparasitics discovery for small R&D labs

Jessica Konijnenburg, Marnix Vlot, Koen Dechering, Rob Henderson, Martijn Vos

TropIQ Health Sciences, Nijmegen, The Netherlands

E-mail: m.vlot@tropiq.nl

The integration of high-profile technologies like machine learning, computer vision, lab automation, and 3D printing into small research and development settings offers transformative potential. The evident advantages of these state-of-the-art tools contrast with the perceived challenges of their implementation in smaller lab environments.

In this presentation, we aim to dispel doubts and demonstrate that such advanced technologies are not only attainable but also immensely beneficial for small-scale R&D labs focused on antiparasitics discovery. Through a series of illustrative examples, we will highlight the successful integration of such technologies showcasing that they are not only attainable but also immensely beneficial for small-scale R&D labs. We will present a series of illustrative examples demonstrating their practical application:

- Tick Movement Insights: Applying computer vision to decode tick movement, enhancing our understanding of tick repellents mode of action.
- Robotic Automation: Automating tick membrane feeding experiments with the precision of a robotic arm.
- Enhanced Throughput: Achieving a 5x increase in throughput for mosquito membrane feeding experiments through using 3D printing and computer vision.
- Acaricide Assay Innovation: developing forced contact acaricide assays with custom-designed 3D printed components.
- Streamlined Data Analysis: Showcasing the benefits of one-click approach to data reanalysis via an application programming interface (API).

These examples not only illustrate the versatility and impact of these technologies but also provide valuable insights and practical lessons. We aim to inspire and encourage other small R&D labs to embrace and benefit from these cutting-edge technologies, stressing that team size is not a barrier to innovation and efficiency in scientific research.

The hypusine pathway in *Ixodes rizinus*: Cloning and characterization of deoxyhypusine synthase as a novel target for drug discovery to treat and prevent vector borne diseases

Annette Kaiser[1]
Heinz Mehlhorn[2], Timm Mehlhorn-Diehl[2]

[1]Medical Research Centre, University of Bonn, Bonn, Germany
[2]Alpha-Biocare, Neuss, Germany

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Ticks are a group of arthropode vectors that are characterized by transmission of a variety of diseases. In Europe, *Ixodes* is the most important tick due to its wide distribution. It transmits a variety of pathogens like *Borrelia* and the tick-borne encephalitis virus. Since the 20th century, *Ixodes* has significantly spread due to changes in the biodiversity. Thus, there is an urgent need to decrease the tick ubiquity in the environment to control tick-borne diseases.

Deoxyhypusine Synthase (DHS) catalyzes the first step in the post translational modification (PTM) of the amino acid hypusine in eukaryotic initiation factor (eIF5A). Modified eIF5A plays a crucial role in cell proliferation of different parasites [1]. Therefore, we cloned a putative DHS locus of 1095 bp from Ixodes by a reverse genetic approach from total RNA of salivary glands and expressed the protein in *E. coli*. *Ixodes* DHS encodes an ORF of 365 amino acids and is commonly spread in different *Ixodes* (98.36%) and *Ripicephalus* species (99%), and fruit flies (70.92 %). The expressed DHS protein has a molecular weight of 40.88 kD and a determined pI of 5.12. In an activity assay the enzyme shows moderate activity. Based on its 3D structure we intend to evaluate DHS as a novel target to discover potent inhibitors to define its role in infection.

[1] Kaiser A, Agostinelli E. Hypusinated EIF5A as a feasible drug target for Advanced Medicinal Therapies in the treatment of pathogenic parasites and therapy-resistant tumors. Amino Acids. 2022 Apr;54(4):501-511. doi: 10.1007/s00726-021-03120-6. Epub 2022 Jan 9. PMID: 35000000.

Keynote Talk

New drugs for the African Animal Trypanosomiases

Mike Barrett

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Sir Graeme Davies Building, Glasgow G12 8TA, UK

E-mail: Michael.Barrett@glasgow.ac.uk

The animal African trypanosomiases (AAT) impact profoundly on agriculture in sub-Saharan Africa, and also in other parts of the world including Asia and Latin America. A number of different species are responsible for a spectrum of diseases caused by trypanosomes. For the human African trypanosomiases (HAT) a number of breakthroughs in recent years have changed the therapeutic landscape and new, safe and orally available medicines have become available. For the animal trypanosomiases though, progress has been less extensive. This is partly because of biochemical differences between the main species causing AAT, for example a nucleoside transporter responsible for uptake of a number of drugs into the trypanosomes (*T. brucei* subspecies) that causes HAT is missing in *T. congolense* and *T. vivax*, the primary causes of AAT. Nevertheless, advances in genome sequencing, in particular, have shown that the phylogenetic proximity between the different trypanosomes species assures that large areas of biochemical similarity are retained. Large compound screens against *T. brucei* have yielded a number several new chemical classes with substantial anti-parasite activity. Unravelling the modes of action of these new compounds has revealed novel targets such as the cleavage and polyadenylation specificity factor subunit 3 (CPSF3), the proteasome, cyclin dependent kinase, CRK12, and topoisomerase II. Structural similarities shared by the trypanosomal orthologues has enabled the veterinary trypanosomes to be targeted by the same compound classes, through the same mode of action, yielding a possible new dawn in seeking novel therapies to combat the animal African trypanosomiases.

The mRNA decapping enzyme of *Trypanosoma brucei* is a promising drug target

Susanne Kramer[1]

Leticia Pereira[1,2], Paula Castaneda Londono[1], Maria Gorna[3], Martin Zoltner[4]

[1] University of Würzburg, Würzburg, Germany

[2]Carlos Chagas Institute (ICC), FIOCRUZ/PR, Curitiba, Brazil

[3]University of Warsaw, Warsaw, Poland

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Degradation of mRNAs is essential in all eukaryotes and contributes to the regulation of gene expression. The process usually starts with the removal of the poly(A) tail, is followed by the removal of the 5´-cap by a decapping complex and terminates with 5´-3´exoribonucleolytic decay. Kinetoplastids have conserved enzymes for the first and third reaction step but lack orthologues to all proteins of the mRNA decapping complex found in opisthokonts and plants. Instead, the Kinetoplastida decapping complex consists of the ApaH-like phosphatase ALPH1 and several mostly Kinetoplastida-unique proteins: an example of convergent evolution.

ALPH1 is a promising drug target: it is essential in Kinetoplastida, the entire enzyme family of ApaH-like phosphatases is absent in mammalian systems and the enzyme can be purified in an active and soluble form. We have built an international team with a joined expertise in structural biology, drug screening and cell- and molecular biology. We have developed a high throughput enzyme assay and are in the process of screening a variety of available drug libraries in vitro.

Inhibitor fluorination fine-tunes inactivation and induced dimerization of essential oxidoreductases from pathogenic trypanosomatids

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Trypanosomatid diseases affect millions of people worldwide and cause devastating symptoms including death.[1] There are only few drugs available, and the majority have poor efficacy and are highly toxic.[1] Infections with trypanosomatids are a severe public health problem and a financial burden to economies in endemic areas [2]. The causative agents, *Trypanosoma* and *Leishmania* parasites, critically rely on an enzymatic peroxide clearance cascade (PCC) which provides electrons for DNA synthesis and biomembrane protection against oxidative stress [3,4]. Enzymes constituting the PCC are absent in hosts and were shown to be promising drug targets [3-5]. A potent inhibitor for one of these enzymes, the oxidoreductase Tryparedoxin (Tpx) from *Trypanosoma brucei*, was identified in a high-throughput screening [4]. The molecule 2-(chloromethyl)-5-(4-fluorophenyl)thieno-[2,3-d]-pyrimidin-4(3H)-one (para-CFT) covalently binds to the Tpx active site and thus inactivates and dimerizes the enzyme [4,6]. Chemically induced dimerization is a versatile tool to investigate dynamic molecular interactions [7]. We investigated the effects of para-CFT on Tpx from *Trypanosoma cruzi* and pathogenic *Leishmania* parasites and found that para-CFT also dimerizes leishmanial Tpx and inactivates them significantly faster than their trypanosomal orthologues. We also explored the role of para-CFT fluorination on fine-tuning of inhibitory properties, dimer formation and (trypano)-toxicity. We conclude that CFT derivatives, with their versatile thieno-[2,3-d]-pyrimidine scaffold, are a good starting point for fragment-based drug discovery and discuss the potential next steps following a fragment growing approach.

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Co-expression of a cytosine base editor, a T7 RNA Polymerase and a Cas12a nuclease variant enables functional screens in *Leishmania* species

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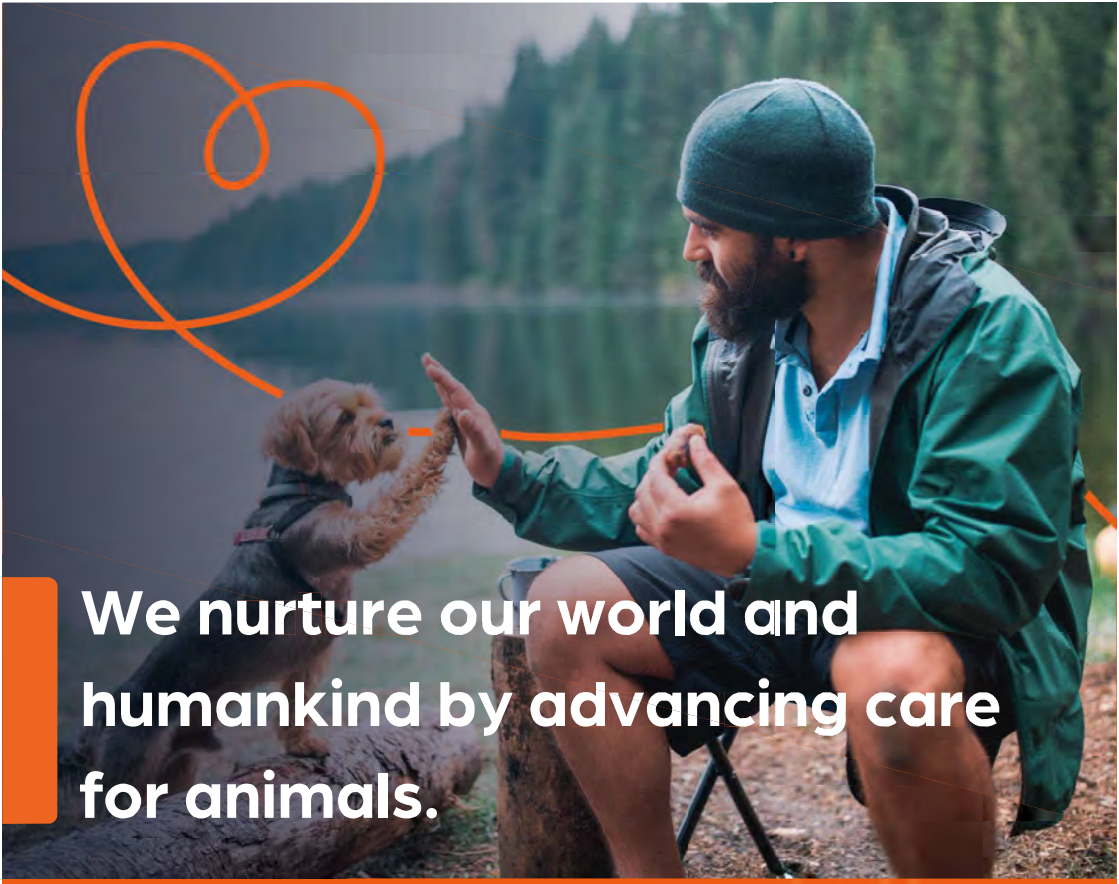
The ability to simultaneously analyse the function of all genes in a genome has obvious appeal. For example, loss-of-function screens can deliver insights into drug resistance mechanisms of any given parasite. Conducting functional genome-wide screens in *Leishmania* parasites, however, has been hindered by limited DNA repair mechanisms. While our previous introduction of a cytosine base editor (CBE) in *Leishmania* showcased the potential for bypassing these limits, challenges remained in achieving high transfection efficiencies, overcoming species-specific editing rates and preventing combinatorial knockdown effects (Engstler and Beneke, eLife 2023). Here, we present an optimized approach to address these limitations.

Firstly, we identified a T7 RNAP promoter variant that ensures stable expression of CBE sgRNAs across *Leishmania* species without affecting parasite growth. Secondly, we generated a triple-expression construct that allows to integrate CBE sgRNA expression cassettes into a *Leishmania* safe harbour locus via AsCas12aUltra mediated double-strand breaks. This boosts transfection rates by up to 100- fold and ensures the integration of only one sgRNA per cell. Finally, we improved our sgRNA design to prioritize edits resulting only in STOP codons. Following these optimizations, we started the first functional genome-wide drug resistance screens in *Leishmania*. In the future, we believe that our im- proved method will enable genome-wide loss-of-function screens in a range of *Leishmania* species, allowing to study the unique biology of this protozoan parasite.



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Heartworm Disease: Drug resistance and the search for new preventives

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Macrocyclic lactones (MLs) are the only pharmaceuticals registered as preventives for heartworm infection, caused by *Dirofilaria immitis*. When ML resistance was first reported, in 2005 - 2015, it was thought to be relatively rare and largely confined to the lower Mississippi Delta region of the USA. However, the risk of resistance is of concern wherever ML chemoprevention is used against heartworm disease. Confirmation of phenotypic resistance is more difficult than assaying for genotypes associated with resistance. Recently, we found alarmingly high levels of resistance in *D. immitis* in parts of the USA. However, analysis of isolates from Europe and Australia suggest that resistance is not yet a problem in those locations. Nevertheless, vigilance is required, and new classes of heartworm preventives are needed.

Heartworm disease prevention is based on preventing the establishment of adult stages of the parasite in the pulmonary vessels and the heart. MLs primarily kill the L3/L4 larval stages. A new approach to interrupting the establishment and transmission of *D. immitis* is to target the regulation of development in larval stages. Depending on the larval stage, in the mammalian host or the mosquito, developmental hormones regulate expression of different genes, and understanding these developmental processes may facilitate the discovery of new chemo-preventives to control *D. immitis* and other filarial infections.

Repurposed drugs that target various stages of filarial worms can support the elimination goals for onchocerciasis

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The Current Preventive Chemotherapy and Transmission Control strategy for onchocerciasis aims to interrupt transmission through annual or bi-annual mass drug administration with ivermectin (IVM). Without available macrofilaricides, however, the adult worms producing microfilariae will survive, underscoring the urgent need for developing macrofilaricides. Importantly, transmission model simulations indicate that the combined use of a hypothetical macrofilaricide (with ~60% efficacy) with IVM would substantially increase the probability of elimination compared with the independent use of each, highlighting a need for alternative integrated treatment regimens.

Using phenotypic screenings of drugs approved for clinical use, we have identified several drugs that can be repurposed for use as therapeutic macrofilaricidal (targeting adult worms and/or embryos) and/or as prophylactic drugs (targeting the establishment of early infections in the host that would have otherwise developed into adult fertile worms). We demonstrated that, 1) Nelfinavir (anti-HIV drug that targets aspartic proteases) significantly inhibited motility of *Brugia pahangi* female worms in vitro and reduced survival of adult worms as well as their fecundity in vivo; 2) Niclosamide and Rottlerin (autophagy inducing drugs) significantly reduced *Wolbachia* levels in vitro and in vivo, and embryogenesis and fecundity in female *B. pahangi* worms in vivo; and 3) Emodepside (repurposed macrofilaricide under clinical development), when used as a prophylactic drug, inhibits molting and motility of *O. volvulus* and *B. pahangi* early stages of the parasite in vitro with IC50s in the nanomolar range.

Our findings indicate that a major programmatic shift that incorporates integrated control strategies, aimed at reducing both the overall adult worm burden and transmission, is needed to achieve the 2030 WHO elimination of transmission goals for onchocerciasis.

Transcriptomic analysis unveils potential novel control targets for filarial nematode infections

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Filarial worms pose a significant threat to human and animal health. The small arsenal of drugs and the growing concern of drug resistance highlight the need for new targets. *Brugia pahangi* and *Dirofilaria immitis*, two closely related nematodes, cause filariasis in cats and dogs, respectively. Despite decades of research, the molecular mechanisms underlying filarial nematode development are poorly understood.

Parasite transcriptomic analyses have enabled the prediction of novel drug targets. We are using *B. pahangi* as a model for *D. immitis*. RNA-seq data were generated for different life cycle stages of *B. pahangi* and differential expression analyses identified a small number of genes upregulated following infection of the mammalian host. Validation of these as possible targets and screening of potential therapeutics would benefit from an improved in vitro culture system. To this end, *B. pahangi* L3 to L4 development in vitro was optimized by the addition of 75 µM ascorbic acid (AA) at day 5.

Most selected genes are novel to filarial nematodes and further validation of their potential as control targets is required. Silencing of control and target genes is being attempted by RNAi with validation by RT-qPCR, while the expression pattern of the proteins is being examined. While providing proof of principle, this approach requires further optimization for robust gene function interrogation and determination of any potential phenotypes.

Pan-Nematoda potential of small molecule inhibitors of PIM kinases as new class of oral anthelmintics

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Parasitic intestinal nematodes infect nearly two billion people worldwide causing significant morbidity, perpetuation of poverty, and loss of life. The limited number of available effective drugs coupled to rapidly expanding drug resistance presents an urgent need for drugs with different mode of actions.

Using systems biology and evolutionary principles, we identified conserved chokepoint enzymes, leading to our central hypothesis that compounds which inhibit conserved chokepoints have strong potential for broad control of diverse nematodes. Phenotypic screening of species at the extremes of the phylogeny with small molecule inhibitors validated our predictions, with PIM kinase inhibitors being established as a new class of kinase targeted anthelmintic drugs. PIM kinase inhibitors, SGI-1776 and CX-6258, and many of our new synthetic analogues designed for improved anthelmintic activity, displayed potent inhibition of motility in two gastrointestinal nematodes, with some also active against filarial species and thus presenting pan-Phylum potential. In addition to increased potency, compound solubility, cellular permeability, and bioaccumulation in the worms directed the design of improved compounds having extended exposure in the mouse intestine. Transcriptome analysis identified several functional modules of significant drug-responsive genes. Finally, we demonstrated that CX-6258 acts as an oral anthelmintic that significantly reduces whipworm worm burden (61%, P =0.0234) and eggs in feces (86%, P =0.0201) in mice.

Our results show that utilizing pan-phylum conserved chokepoint therapeutic targets can lead to the novel discovery and development of drugs with broad-spectrum efficacy against nematodes.

Action of 5-aminovalerate on GABA-gated channels from chicken and its parasite *Ascaridia galli*

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The gut-brain axis, a bidirectional communication system linking the gut microbiota and its metabolites to the central nervous system, has been extensively explored in mammals but remains relatively uncharted in poultry. Our investigation into the gut-brain axis in chickens involved the analysis of caecal contents from both conventional and germ-free birds, revealing a significant influence of the gut microbiota on 5-aminovalerate (5-AV) concentrations in the caecal compartment. 5-AV is a derivative of gamma-aminobutyric acid (GABA), the principal neurotransmitter in mammalian and avian central nervous systems. While GABA supplementation in chicken feed has demonstrated protective effects on the intestinal mucosa, the specific role of 5-aminovalerate remains undefined. RNAseq analyses in the caecal tissue uncovered genes coding for GABA receptors in the caeca of chickens. Furthermore, we demonstrated the modulatory effect of 5-AV on GABA heteromeric receptors expressed in *Xenopus* oocytes using two-electrode voltage clamp experiments. Finally, our research extended to the exploration of 5-AV sensitivity of the GABA receptors from the chicken helminth *Ascaridia galli*, suggesting potential co-evolution relationships between the gut microbiota, the chicken, and the worms they harbour. These findings open avenues for novel anti-parasitic strategies and innovative probiotic solutions aimed at enhancing chicken health and welfare in commercial poultry.

Multi-species nematode screening uncovers new classes of broad-spectrum anthelmintic compounds

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Parasitic helminths are a major global health threat, infecting nearly one-fifth of the human population and causing significant losses in livestock and crops. New anthelmintic drugs are urgently needed, as resistance to existing drugs is emerging. Using the NYUAD High Throughput Screening platform, we screened ~50,000 compounds for broad anthelmintic properties while being non-toxic to human cells. The screen identified most known anthelmintics and additionally ~150 compounds with no previously reported anthelmintic activity. Among these, four related natural compounds caused dose-dependent lethality in *Caenorhabditis elegans* and *Pristionchus pacificus* across all developmental stages, including dauer and embryos, while being relatively well tolerated in mammalian cells. These molecules also caused mortality in direct testing on three veterinary parasitic nematode species: the multidrug resistant *Haemonchus contortus* UGA strain (ruminants), *Teladorsagia circumcincta* (sheep and goat) and *Heligmosomoides polygyrus* (rodents). In vivo preclinical trials in mice infected by *Heligmosomoides polygyrus* helminths further showed that these compounds cause a consistent and significant reduction in *H. polygyrus* egg laying and adult worm load. In-depth phenotypic characterization in *C. elegans* revealed mitochondrial defects, reduced oxygen consumption, diminished ATP levels, and increased reactive oxygen species. Together with genetic and pharmacological perturbations, our results point to lipid metabolism as the key target pathway of this novel cluster of anthelmintic compounds.

Exploring the antiparasitic effects and active compounds of bio-refined *Trifolium pratense* (red clover)

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Background: The global livestock industry is grappling with environmental and infectious disease issues. Recently, biorefining plants to extract valuable feed protein has emerged as a solution, with the potential utilization of by-products like fiber pulp being particularly promising. This study explores the antiparasitic properties of fiber pulp from red clover (*Trifolium pratense*) post-protein extraction, aiming to identify effective compounds.

Method: We examined biorefined red clover from two genetic lines, Callisto and Hammon. The plants were biorefined, producing pulp fiber extracted with 70% acetone. This extract was tested for antiparasitic activity against the helminth *Ascaris suum*. High-performance liquid chromatography (HPLC) was used to microfractionate the extract for bioactivity screening. Effective compounds were then identified using nuclear magnetic resonance (NMR) spectroscopy, and liquid chromatography- mass spectrometry (LC-MS) quantified their concentration changes during biorefining.

Result: The red clover pulp fiber extract exhibited over 90% inhibition of *Ascaris suum* at various concentrations. Biochanin A was identified as the most potent antiparasitic compound, with its concentration notably increasing post-biorefining.

Conclusion: The biorefining process enhances the antiparasitic efficacy of red clover, primarily due to increased levels of biochanin A. This finding underscores the process's potential in unlocking new, valuable properties from plant by-products.

Keynote Talk

Genomic insights into drug response by helminths that infect animals and humans

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Extensive use of drugs to control parasitic worms has led to the rapid evolution of drug resistance in many species. While resistance is particularly evident in some species that infect livestock and other domesticated animals, it remains a credible threat to the control of human-infective species that impact over a billion people worldwide.

Unfortunately, our ability to understand the mechanism by which parasites become resistant, despite great effort, remains limited. We have been developing genetic resources to better understand the biology of helminths and use this as a platform to define the genetic responses of helminths to drug treatment. Using examples from both human and animal infective helminths, I will highlight new insights and lessons learned using genome-wide approaches to understand drug-treatment responses and explore how this information can be exploited to develop better diagnostics and treatments for helminth infections.

Comparative transcriptomic analysis in the *Caenorhabditis elegans* parasite model: impact of NHR-8

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The development of resistance to antiparasitic drugs, such as ivermectin, poses a significant challenge for the agricultural industry and global human health. It is imperative to enhance the efficacy of existing drugs by identifying new targets against resistance. Among various resistance mechanisms, highly conserved nuclear receptors in nematodes play a role in biocide resistance by regulating the expression of genes in drug detoxification systems. We have demonstrated that the NHR-8 receptor in nematodes, which regulates lipid homeostasis, also influences the tolerance and the development of resistance to ivermectin. The strategic importance of this receptor makes it a pertinent target for combating pathogens and enhancing the effectiveness of existing drugs.

We possess several original strains of the parasitic nematode model *Caenorhabditis elegans* invalidated for NHR-8. Using an RNA-seq transcriptomic approach, we confirmed the involvement of NHR-8 in regulating genes related to stress response, detoxification, and metabolism in the context of ivermectin-resistant or wild-type strains. In addition to underscoring the significance of NHR-8 in ivermectin resistance, this work will contribute to our understanding of the complex transcriptomic regulation controlled by the still poorly understood NHR-8 receptor.

Leveraging proteomics, bioinformatics, and ecotoxicology models to select new targets overcoming *L infantum* drug resistance

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The excessive use of the few available antileishmanial agents has led to the emergence of highly-resistant *Leishmania infantum* strains, resulting in untreatable infections, therapeutic failure, and exacerbating the chronic burden of the disease. This topic has a significant impact on human and animal health in endemic regions worldwide, and in areas where dogs and other sylvatic animals serve as reservoirs for infection. There is an urgent need to design and develop new drugs to fight and overcome drug resistance, as the commonly used antimonials, paromomycin, and miltefosine show lower efficacy. Recent advancements in Vector-Borne Parasitic Diseases research have also highlighted and increased the consideration of environmental drug safety and their ecotoxicological impact, while simultaneously focusing on understanding and preventing resistance issues from the outset of the drug discovery projects[1]. To address this challenge, the exploitation of brand-new technologies like high resolution Mass Spectrometry and bioinformatic/ecotoxicology predictive models, can help identify the proteins and metabolic pathways modulated in the parasite during the infection phase, and suggest new drug targets and innovative drug combination strategies. Herein, we have investigated the biochemical mechanisms of resistance to sodium stibogluconate, paromomycin, and miltefosine[2] in three distinct parasitic strains derived from human clinical isolates. Human immortalized THP-1 cultures were infected with the resistant *Leishmania* parasites to mimic the acute phase of the infection, and were submitted to bottom up, whole-cell LC-MS/MS proteomics pipeline. Among the identified proteins of differentially expressed proteins (DEPs), the 14 DEPs identified, only peroxiredoxin emerged in all resistant strains. DEPs profile was compared with their mRNA expression profile, and finally functional association networks tools allowed the comparison of parasitic to human proteomes. Guest-host cross talking proteins and pathways were well defined to discard those proteins/pathways involved in both the human and parasitic networks. To assess the environmental impact of the remaining proteins, a SeqAPASS analysis was employed to predict cross species homology and drug target susceptibility, based on the evolutionary conservation of protein. The MATH domain-containing protein, ATP-binding cassette B2, histone H4, calpain-like cysteine peptidase, and trypanothione reductase emerged as top candidates. In an optic of a drug discovery program driven by One Health approach, by exploiting bioinformatic tools and predictive ecotoxicological platforms, we propose the above-mentioned target to undergo further molecular investigation to be considered to overcome parasitic drug resistance.

[1] COST ACTION CA21111 www.onehealthdrugs.com
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Assessing the propensity of selecting mutant parasites for the antimalarial drug cabamiquine

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Plasmodium falciparum drug resistance poses a constant threat as it can lead to the demise of first-line treatments. It is therefore critical to monitor this parameter during anti-infective drug discovery and development. Here, the propensity of the antimalarial agent cabamiquine, an exquisitely potent inhibitor of *P. falciparum* eukaryotic elongation factor 2 (PfeEF2), to select for resistant *P. falciparum* parasites was assessed by analyzing pre-clinical and Phase I clinical trial data. Mathematical modelling of these data using both deterministic and stochastic models allowed us to estimate the frequency of parasite resistance to cabamiquine across different in vitro (including field isolates) and in vivo infection models. This modelling was also used to predict the likelihood that these mutants either emerged de novo following drug treatment or alternatively were likely present at the time of treatment (pre-existent). Finally, a homology model of PfeEF2 was built to describe the known mutant parasites and provide further insights to the binding mode of cabamiquine.

A novel approach to control intestinal parasites - "Fermented anthelmintics"

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Bt Crystal proteins have until recently been used commercially exclusively for control of insect pests and account for 90% of the biopesticide market. Our group has spearheaded efforts to bring Cry proteins into clinical/commercial use against nematode pests, with Cry5Ba being our lead candidate. Gastrointestinal nematode (GIN) parasites are critical targets in both human health, with >1.5 billion people infected, and animal health (e.g., sheep, pigs, horses, dogs, cattle) for which nematode parasites are nearly ubiquitous. In addition, GIN resistance in human and animal health to currently used drugs is increasing. Thus, there are commercial opportunities for Cry proteins to make a difference as anthelmintics. Because ingestion of a Cry protein therapeutic to cure a GIN infection in a vertebrate is different than use of Cry proteins to control insects, we have had to develop a novel Cry protein path for commercialization. Here we will discuss the development of a new fermentable production and delivery method for Cry proteins suitable for therapeutic oral dosing, which we call IBaCC (inactivated bacteria with cytosolic crystals). Studies have been performed in small and large animals (rodents, sheep, horses, pigs) to show we can successfully scale up production of highly bioactive Cry5Ba IBaCC therapeutics that can cure a wide range of GIN infections. Studies have also been performed to validate the safety and direct targeting of IBaCC. We have also tested Cry5Ba IBaCC against multidrug resistant hookworms and expanded activity against whipworms. In addition to Cry5Ba, we have now identified five other Cry proteins that can cure parasitic GIN infections in vivo. Studies examining the impact of Cry protein combinations are beginning with the ultimate aim of producing a combination anthelmintic within a single fermentation that is potent and that inhibits parasite resistance. Together, these studies are providing the framework for an evolution in the use of Cry proteins from insect control towards human and animal anthelmintic therapeutics.

The tortoise and the hare: a characterization of two schistosome TRPM ion channels

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Recent data have identified two schistosome transient receptor potential ion channels of the melastatin subfamily (TRPM channels) that mediate worm contraction, tissue depolarization and tegumental damage. One channel is activated by praziquantel (TRPM-PZQ [1]) and one channel is activated by meclonazepam (TRPM-MCLZ [2]) – chemotypes with well-known anthelmintic properties. However, a key difference between these ligands is their differential activity against juvenile schistosomes, with MCLZ showing greater efficacy than PZQ versus this life cycle stage. What is the basis for this difference? Is it a property of ligand exposure to the target, or is it an intrinsic property of the target itself?

Here, using unique channel activators, we show that intrinsic properties of the target are critical. While TRPM-PZQ (the proverbial 'hare') can mediate a large non-selective cation flux and fast cellular depolarization (single channel conductance =250pS under specific recording conditions) – under physiological conditions - TRPM-PZQ activity is subject to a reversible Ca^{2+}-dependent inactivation such that channel activity is exhausted allowing cellular recovery. In contrast, TRPM-MCLZ (the proverbial 'tortoise') displays a considerably smaller single channel conductance (=30pS). Nevertheless, the resulting cellular depolarization is more profound on account of both unique ionic selectivity, and a lack of Ca^{2+}-dependent inactivation. This likely ensures cellular Ca^{2+} overload and toxicity. These data demonstrate unique functional properties of these TRPM siblings.

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Stuck in a toxic relationship: hERG and cytotoxicity mitigation in schistosomiasis drug discovery

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Schistosomiasis is the second most prevalent neglected tropical disease, with around 700 million people at risk worldwide [1]. It is a parasitic disease caused by blood flukes of the genus *Schistosoma*. Infective larvae reside in an intermediate host before penetrating the skin of the human host where the adult worms mature. Eggs laid by the females can become trapped in surrounding tissues resulting in an inflammatory response. Chronic infection can cause urogenital disease or bladder and cervical cancers [2]. Treatment of schistosomiasis relies on the administration of praziquantel. This is safe and efficacious against, only, the adult worms of all six *Schistosoma* spp [3]. Reliance on a single drug and mass drug administration protocol poses a threat to the public health system as development of resistance becomes a risk. The possibility of this resistance rising to clinically significant levels has motivated the scientific community to search for new drug nominees [4].

At the Universities of Dundee, Aberystwyth, and Cardiff, we have now established an integrated drug discovery pathway and developed an assay cascade to progress compounds with anti-schistomal activity against *Schistosoma mansoni*. Key requirements for new treatments include multi life cycle stage activity, suitable properties for oral administration, and low risk of toxicity or off-target effects. Alongside international schistosomiasis collaborators, we are currently working towards a suitable target product profile for future treatments [5].

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Targeting of *Schistosoma mansoni* c-Jun N-Terminal Kinase JNK by type II-kinase inhibitors with potent antischistosomal activity

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Schistosomiasis has for many years relied on a single therapeutic drug, praziquantel, and an alternative treatment is needed. *Schistosoma mansoni* c-Jun N-terminal kinase (SmJNK) is a MAP kinase that plays a key role in parasite maturation, reproduction, and survival. Although much effort has been invested in the discovery of protein kinase (PK) inhibitors, the majority are still not targeted by an inhibitor with a useful level of selectivity. In contrast to type I inhibitors, type II PK inhibitors bind PKs in the so-called DFG-out conformation, corresponding to the inactive state of the enzyme. This binding is characterized by a higher selectivity. Therefore, we performed a virtual compound screening against the ATP pocket of JNK in the DFG-out conformation. Atomwise has provided 85 compounds predicted to target SmJNK as type II inhibitors. We have screened these selected compounds in vitro against schistosomula of *S. mansoni* using the XTT assay. Adult worms were screened and assessed for motility, attachment, and pairing status. Thirty-three compounds were active in at least one of the assays and two compounds presented strong effects against both life stages. Phenotypic alterations caused by active compounds were analysed by confocal microscopy. In conclusion, the approach to screen type II kinase inhibitors resulted in the identification of two potent compounds that can be further developed against schistosomiasis.

Recent progress in the treatment of soil-transmitted helminthiasis

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Millions of people are infected with soil-transmitted helminths, resulting in anaemia, malnutrition, growth stunting, and cognitive deficits. The current control strategy of the World Health Organization to reduce the burden and morbidity of these infections is preventive chemotherapy, i.e. the administration of the two benzimidazoles (albendazole and mebendazole) using single, oral doses to at risk populations, mainly children without prior diagnosis. Both benzimidazoles are highly efficacious against *Ascaris lumbricoides*, but only albendazole is efficacious against hookworm, and both drugs are unsatisfactory against *Trichuris trichiura* infections. Drug combinations as albendazole-ivermectin and albendazole-moxidectin result in superior efficacy against *T. trichiura*, but not in all settings. Different strains of *T. trichiura* might be responsible for the varying efficacy. Moreover, we have recently shown that the gut microbiome might be influencing the efficacy of albendazole-ivermectin. Therefore, there is a need to engage in research and development for new anthelminthic drugs. The recent highly encouraging results with emodepside in Phase 2a and Phase 2b clinical studies hint that this drug might become a game changer in the treatment for soil-transmitted helminth infections.

Genetic makeup of a *Trichuris species*, not responding to drug treatment in Côte d'Ivoire and potential drug targets from comparative genomic analyses

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Soil-transmitted helminth (STH) infections affect up to 1.5 billion people worldwide. If untreated, STH infections can cause severe long-term morbidity. The whipworm *Trichuris trichiura* is one of the most prevalent STH species. However, the widely used anthelmintics, albendazole and mebendazole show low efficacy for *T. trichiura*, with a decrease over the past 20 years. In a recent phase 3 clinical trial, albendazole-ivermectin, the currently best treatment available, revealed a cure rate of mere 14% in Côte d'Ivoire compared to Laos and Pemba, Tanzania with cure rates of 66% and 49% respectively [1].

To gain insight into the genetic makeup of the *Trichuris* species in Côte d'Ivoire, 1143 whipworms from humans and swine were collected and sequenced. Phylogenetic analysis confirmed the existence of a new Trichuris species, naturally infecting humans, genetically closer to *T. suis* and apparently resistant to combination therapy. Hybrid de-novo whole genome assembly and gene prediction using the braker2 pipeline, allowed the identification of 14897 genes in 8001 orthologous groups. Leveraging the close genetic relationship with *T. suis*, by looking for genes that are shared with *T. trichiura* and do not occur in *T. suis*, transcripts were identified, that play a crucial role in human infection and are suitable drug targets or vaccine candidates. Amongst the identified transcripts are serpins, tetraspanins and trypsin like serine proteases.

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Identification of a novel, multi-stage anti-schistosomal derived from mouse serum

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Praziquantel (PZQ) is the drug of choice for the treatment of schistosomiasis. However, PZQ solely targets the adult worms, the widespread use of PZQ also favors the risk of the development and spread of drug resistance. There is a need to develop novel drugs effective against immature, juvenile and adult worm stages. We recently demonstrated the presence of soluble multi-stage schistosomicidal factors in the serum of mice. The aim of the present study was to build on these findings to identify the active compound(s) in mouse serum and characterize the anti-schistosomal properties. We used large scale fractionation of mouse serum to investigate the susceptibility of all schistosome stages in our novel in vitro culture platform. Subsequent comparative mass spectrometry analysis revealed a set of candidates that we selected based on enzymatic properties and screened for their multi-stage schistosomicidal efficacy. Through in vitro screening, we observed that a certain phospholipase shared a similar schistosome killing phenotype with mouse serum. This phospholipase lethally affected parasites at all stages, including ex vivo adult worms. Overall, our data present a multi-stage schistosomicidal host component, likely produced in response to infection which could be explored further for the development of novel therapeutic strategies.

Anthelmintic natural product discovery using *Caenorhabditis elegans* and *Schistosoma mansoni* screenings

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Infection with the blood fluke (schistosomiasis) is one of the most devastating human parasitic diseases [1]. The drug Praziquantel was introduced in the 1980s and is up today the only therapeutic agent available. Nowadays, decreased drug efficacy, that might be linked to resistance development, is observed in endemic regions [2]. Hence, novel anti-schistosomal drugs are urgently needed. Natural products have played a major role for drug discovery ever since and thereby represent a promising source [3].

In this project, organic extracts from bacterial and fungal strains have been tested for anthelmintic activity against *Schistosoma mansoni*. Rearing of this parasite is labor-intensive, thus *Caenorhabditis elegans* was evaluated as a surrogate for anti-schistosomal screenings. Dose response assays allowed prioritization of extracts showing the strongest activity (lethality with-in 72 h at 0.25-fold extract concentration). Out of 1500 extracts screened against *C. elegans*, 1.7% showed strong activity. Activity against *S. mansoni* was confirmed for 15.4% of the *C. elegans* hits. In comparison, our initially untargeted primary screening against *S. mansoni* (750 extracts) showed a hit rate of 3%“. The most promising extracts were subjected to UPLC-MS/MS coupled bioactivity-guided micro-fractionation to identify the activity-causing compound(s). In the active fractions, no literature-known compound could be dereplicated. Hence, cultivation conditions were optimized to enable compound isolation and subsequent structure elucidation. Latest screening results and the compound characterization status will be reported.

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Characterization of anthelminthic properties of plants from Mayotte island

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Plants are a major source of anti-infectious compounds of interest for animal and human health. Mayotte is a French Department from European outermost regions, located in the Indian sea. Mayotte island has a great diversity of plants traditionally used in the local Pharmacopoeia for their anti-infectious activities. Gastro-intestinal nematode (GIN) parasites are a serious issue for livestock industry due to production losses and veterinary costs, along with growing development of anthelmintic resistance. In order to find alternative strategies for the control of GINs, we screened the anthelmintic potential of 17 plants of medical interest collected in Mayotte. Aqueous extracts were prepared and assessed on the sheep GIN *Haemonchus contortus* and the chicken GIN *Ascaridia galli*, using hatch assays, larval development tests and automated larval migration assays.

None of the 17 plant species showed any ovicidal activity. Interestingly, 3 of the plant species significantly inhibited the larval development of *H. contortus* or *A. galli*. In addition, 4 plant extracts significantly inhibited the migration of *H. contortus* larval stage. These promising results validate the anti-parasitic potential of exotic plants from Mayotte and open the way to deeper investigations in vivo, together with the identification of the bio-active compounds.

Serotonergic signalling modulates movement and growth in juvenile liver fluke, *Fasciola hepatica*

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Fasciola spp. liver fluke are helminth pathogens with global impacts on human and animal health. Anthelmintic resistance threatens fluke control such that there is a clear need for the development of novel flukicides. Classical neurotransmitter pathways are a target for a range of successful anthelmintics, but remain an untapped source of potential targets for flukicide development. Serotonin is the most prominent excitatory neurotransmitter in flatworms and has been intrinsically linked to regulating neuromuscular control. This study utilises our functional genomic platform to interrogate serotonergic signalling in liver fluke, F. hepatica and assesses its potential as a target system for control. Bioinformatic analysis characterised a complete serotonergic signalling pathway for liver fluke and analysed a broader serotonin GPCR complement for clinically relevant flatworm species. Localisation methods revealed widespread expression of serotonin and serotonin signalling components within the liver fluke central nervous system. RNA interference of signalling pathway components, including five putative serotonin GPCRs, suggests removing serotonin from a synapse negatively impacts juvenile motility, growth and development. RNAi phenotypes were validated through exogenous application of serotonin and selective serotonin reuptake inhibitor (SSRI) compounds. These data support the hypothesis that serotonin signalling plays a role in the modulation of motor function and exposes a novel link between serotonin signalling and juvenile fluke growth, encouraging the exploitation of serotonin-associated drug targets for flukicide development.

Triggering apoptosis in juvenile liver fluke – a novel strategy for control?

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The liver fluke, *Fasciola hepatica*, places a significant disease burden on ruminant livestock worldwide and causes a neglected tropical zoonosis. Reports of flukicide resistance are increasing, such that there is a pressing need for novel drug target discovery and validation. A delicate balance between cell survival and programmed cell death mediates the cellular turnover that supports tissue homeostasis and growth. A key facet of juvenile *F. hepatica* virulence is their ability to rapidly turnover various cell and tissue types, a process driven by neoblast-like cell proliferation. As such, dysregulating neoblast-like cell biology represents an appealing avenue for control. In silico analyses revealed that *F. hepatica* possesses the core machinery required for a functional intrinsic apoptotic pathway, in addition to key components of major pro-survival signalling pathways known to promote cell proliferation/survival in higher organisms. The RNAi-mediated silencing of putative apoptotic kinases profoundly inhibited juvenile growth, coupled with elevated levels of apoptosis and a temporal shift in cell proliferation levels. This ultimately proved fatal. Transcriptomic analyses of apoptotic kinase-silenced juveniles provided further insight into the molecular mechanisms underpinning RNAi phenotypic readouts. These data indicate that the dysregulation of cell cycleapoptosis interplay represents a novel approach to undermine the virulence of pathogenic juvenile *F. hepatica*, underscoring the appeal of pro-survival signalling pathway components as targets for novel flukicide development.

FasciolOmics - Omics-driven discovery of drugs and drug targets against liver flukes

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Knowledge on the cell type-specific gene expression repertoire of multicellular parasites facilitates a more targeted discovery of genes with vital functions. We established a cell and tissue atlas of gene expression for the zoonotic liver fluke *Fasciola hepatica* by applying single-cell (sc) transcriptomics and spatial transcriptomics (ST) technologies (10x Genomics). Differential gene expression analysis identified 14 cell clusters among 27,000 cells by scRNA-seq and eight different tissue types by ST, covering in total over 9,000 genes. This allowed us to interrogate the gene expression of cells critical for parasite survival, including gastrodermal cells, stem cells, tegumental and neuronal cells. We revealed a cell type- or tissue type-specific expression of several known and new putative drug target genes (ß-tubulins, protein kinases, a nuclear receptor (NR) and calcium channel) as well as drug resistance genes (GSTs, ABC transporters). Target gene prioritization and functional characterization using RNA interference and small-molecule inhibitors identified an intestinal NR and a tegumental PK with importance for worm survival. Given the essential roles of PKs in cellular processes, we furthermore curated the full kinome of *F. hepatica* using a genomic-phylogenetic approach. We annotated 245 PKs and prioritized 11 PK inhibitors, among which some were at least as potent as triclabendazole against in vitro-cultured immature and adult parasites. Taken together, our new omics datasets can serve as playground for the discovery of druggable genes in this parasite.

Application of RNA technologies for improved control of cystic echinococcosis

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Cystic echinococcosis (CE) is a worldwide parasitic disease caused by the larval stages of the tapeworm *Echinococcus granulosus*. To date, the control of CE has been a public health priority due to the difficulties in diagnosis and treatment. Although therapeutic agents exist, e.g. benzimidazoles to treat intermediate hosts, these approaches have shown little efficacy. Therefore, novel chemotherapy alternatives and drug targets are urgently needed to improve control programs against CE.

Non-coding RNAs have been identified as potential diagnostic targets and therapeutic candidates for parasitic infections. Previous studies have shown that some miRNAs, including mir-71, are involved in parasite development, in hydatid cyst fertility and in the establishment of successful infection in the experimental host. In line with this, a study was launched with the aim to discover potential new targets for the development of a new therapeutic approach against CE, through a methodological approach consisting of different work packages involving the collection and analysis of hydatid cysts, eggs, and adult parasites, as well as careful procedures for the extraction and analysis of RNA.

The results of this study could form the basis for the development of innovative strategies based on RNA technology to control CE and reduce the global health burden. Finally, the novel approaches developed using *Echinococcus* as a "model parasite" could also be used to control other parasitic infections.

Investigation of the threonine metabolism of *Echinococcus multilocularis*: EmTDH as a potential drug target against alveolar echinococcosis

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Metacestodes of *Echinococcus multilocularis* cause the severe zoonotic disease alveolar echinococcosis for which novel treatment options are urgently needed. In vitro experiments showed strong scavenging of threonine by *E. multilocularis* metacestode vesicles.

We measured significantly increased growth for L-threonine-treated metacestode vesicles in vitro. Germinal layer (GL) cells treated with L-threonine formed increased numbers of metacestode vesicles, whereas the threonine analogue 3-hydroxynorvaline reduced this number. Tracing of 13C4-L-threonine showed that in vitro cultured metacestode vesicles consume threonine and metabolize it to glycine, which indicates a functional threonine dehydrogenase (TDH) pathway. Q-RT-PCRs confirmed high expression of EmTDH in metacestodes in vitro and in mice, and the respective native protein was enzymatically active. We tested several TDH inhibitors in enzymatic assays on recEmTDH. Active compounds were further tested in a damage marker release assay on *E.multilocularis* metacestode vesicles and in a cell viability assay on GL cells. Sanguinarine showed activity and was further characterized by calculating IC50 values against metacestode vesicles, GL cells and mammalian cells to evaluate cytotoxicity.

Our experiments provide evidence that threonine metabolism is important for *E. multilocularis* and that it is mediated via EmTDH. Inhibiting this metabolism could provide new treatment options as human TDH is non-functional. The here established enzymatic assays could serve for medium-throughput screening of potential other inhibitors targeting the threonine metabolism of *E. multilocularis*.

Target-based design of metabolically stable cestocides

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The anthelmintic drug praziquantel (PZQ) has been used for decades to treat parasitic flatworm infections of clinical and veterinary importance. Recent identification of TRPMPZQ, a parasite target of PZQ [1], has enabled target-based design opportunities to develop novel anthelmintic chemotypes [2]. Two tantalizing approaches are exploitation of (i) binding pocket variation between parasite TRPMPZQ orthologs to target specific diseases [2, 3], and (ii) metabolically stable PZQ derivatives to prolong target exposure [4]. The latter is challenging for trematode TRPMPZQ, as metabolically stable derivatives resulting from cyclohexyl ring modifications typically lose potency at TRPMPZQ owing to the stringent binding pocket architecture [5].

Here, we capitalized on both these strategies to develop potent, metabolically stable ligands targeting cestode TRPMPZQ. First, cyclophyllidean cestodes possess a histidine residue at a critical position in the binding pocket that can be exploited to enhance ligand potency. Second, a further amino acid difference from trematode TRPMPZQ makes the cestode TRPMPZQ binding pocket more sterically accommodating. This allows incorporation of modifications that show greater metabolically stability than PZQ. Pursuing both these target-based design opportunities led to the identification of PZQ derivatives that showed improved potency at cestode TRPMPZQ and stability in vitro. Based on these improvements, testing these analogs against various cestode ex vivo and in vivo models has merit.

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Precision designed anti-pathogen drugs

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The microtubule cytoskeleton, a critical component in the intricate machinery of living organisms, plays a vital role in cell structure, division, transport, tissue development, and neuronal function. This microtubule cytoskeleton is composed of microtubules which are polymeric filaments made from a protein called tubulin. Proper microtubule structure and function is indispensable for any organism. Perturbing microtubule function by using small molecule compounds that bind to its constituent tubulin protein is highly toxic for the cells. This characteristic of tubulin-binding compounds has yielded extensive applications, including their role as anti-cancer agents (e.g. paclitaxel) and, in specific cases, as antiparasitic treatments (e.g. fenbendazole), highlighting the credibility of this intervention strategy. Importantly, although tubulin is a conserved protein present in all eukaryotic cells, there exist differences in tubulin between different species. Therefore, an ability to design species-specific drugs that could differentiate between pathogen and host microtubule cytoskeleton, disrupting the tubulin of only the pathogen have the potential to revolutionize the way we manage infectious diseases. Such a technology offers a valuable source of potential drug Leads. At ASTRA Therapeutics, we have mastered the art of selectively targeting microtubules from eukaryotic pathogens. With our ParaX® Drug Discovery Platform, we have perfected the technology to exploit the subtle differences between pathogens and hosts by precision atomic scale drug engineering, to develop safe and potent anti-pathogen drugs that we call the Parabulins®. During this presentation, we will elucidate the significance of targeting tubulin in pathogenic organisms and explore how ParaX® is poised to harness this potential by advancing the development of Parabulins® for the treatment of diverse pathogens affecting humans, animals, and plants.

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Evaluation of the trithiolato-bridged arene ruthenium complex conjugated to 9-(2-hydroxylethyl)-adenine (OD62-18) as a potential treatment for *Toxoplasma gondii* infection.

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The apicomplexan parasite *Toxoplasma gondii* is a major food-borne pathogen, causing toxoplasmosis. Current treatment options are limited due to suboptimal efficacy and adverse side effects. From a library of > 300 organometallic drugs, we explored the therapeutic potential of a trithiolatobridged arene ruthenium complex conjugated to 9-(2-hydroxyethyl)-adenine (OD62-18).

OD62-18 inhibited parasite proliferation in vitro with an IC50 < 60nM, induced significant alterations in the mitochondrial matrix and the disappearance of cristae, and had a negative impact on the mitochondrial membrane potential, while the overall morphology and secretory organelles were not notably affected. Differential affinity chromatography and mass spectrometry identified the YOU2 family C2C2 zinc finger protein, a Tim10 homologue, as the primary OD62-18 binding protein. However, knockout parasites lacking TgTim10 displayed no discernible differences in growth, proliferation, or plaque formation, and maintained a similar IC50 under OD62-18 treatment.

OD62-18 treatment of *T. gondii* oocyst infected mice resulted in only negligible effects on parasite load in various tissues, and inductively coupled plasma mass spectrometry (ICP-MS) analysis revealed predominant drug excretion after 24 hours, with no penetration into the brain.

While OD62-18 demonstrates notable in vitro efficacy against *T. gondii*, further investigations are necessary to address the observed in vivo limitations and optimize its therapeutic potential.

Assessment of triclabendazole treatment against *E. multilocularis*

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Echinococcus multilocularis, the causative agent of the severe zoonotic disease alveolar echinococcosis (AE), currently presents treatment challenges due to its high regenerative potential, rendering conventional benzimidazole-based chemotherapy parasitostatic [1, 2]. The urgent need for novel, parasiticidal treatment options led us to evaluate various benzimidazoles against in vitro cultured *E. multilocularis* metacestodes and isolated germinal layer cells that are involved in the parasite's regeneration.

Triclabendazole (TCBZ) herein displayed promising in vitro parasiticidal activity. Consequently, a study in the secondary AE BALB/c mouse model was undertaken, employing micropipette-guided drug administration, a method for voluntary drug ingestion in mice [2]. Treatments included placebo, albendazole (200 mg/kg), triclabendazole (100 mg/kg), and alternating albendazole/triclabendazole (2 weeks/1 week) for 12 weeks. Assessments of treatment efficacy encompassed parasite weight, ultrastructure, resected parasite material viability in vitro, and drug metabolite levels in blood plasma measured via ultra-high performance liquid chromatography-MS/MS.

TCBZ treatment alone did not lead to a reduced parasite burden or parasite viability compared to the placebo control and combined treatment did not exhibit enhanced efficacy compared to albendazole treatment alone. Histological assessments of mouse organs post-treatment revealed no significant alterations. However, the pharmacokinetic profile highlighted distinct features of TCBZ, exhibiting slower metabolism and more efficient uptake into the bloodstream, resulting in increased concentrations of the active metabolite, triclabendazole-sulfoxide, in blood plasma. Follow-up investigations aim to address the current lack of TCBZ efficacy in the AE mouse model.

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[2] Brehm, K., Koziol, U., 2014, Parasite 21, 72. https://doi.org/10.1051/parasite/2014070
[3] Scarborough J et al. 2020, Brain Behav Immun. Aug;88:461-470. doi: 10.1016/j.bbi.2020.04.015. Epub 2020 Apr 9. PMID: 32278850.

In vitro drug screening cascade for *Echinococcus granulosus*

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Echinococcus spp. cause the severe zoonotic diseases alveolar echinococcosis (AE) and cystic echinococcosis (CE), for which new treatments are urgently needed. An in vitro drug screening pipeline had been established for AE, whereas to date drug efficacy assessments for CE have relied mostly on the subjective eosin exclusion test on protoscoleces (PSCs). Thus, there is the urgent need to develop objective tests to identify compounds that are active against *Echinoccocus granulosus sensu stricto* (EG). We applied an in vitro screening cascade originally established for *E. multilocularis* (EM) metacestodes to EG and compared the efficacy of a set of standard drugs (niclosamide, nitazoxanide, albendazole, monepantel, mefloquine, buparvaquone and MMV665807). Drug assessments were carried out by a metacestode vesicle damage marker release assay, a metacestode vesicle viability assay, a germinal layer (GL) cell viability assay, and a PSC motility assay. Our results showed that MMV665807, niclosamide and nitazoxanide are active against both species in all assays. MMV665807 and monepantel were significantly more active against EM metacestode, while albendazole and nitazoxanide displayed higher activity against EM GL cells. Albendazole remained inactive against EG GL cells even after 5 days of treatment. Treatments of PSCs with albendazole and monepantel had no impact on motility in both species.

These results show that our established drug screening cascade can also be applied to EG. This screening cascade will be applied to a larger panel of compounds, such as the medicines for malaria venture pandemic response box consisting of 400 compounds.

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P1

Pre-clinical development of corallopyronin A – update on pharmacology and validation of an amorphous solid dispersion formulation

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Corallopyronin A (CorA) is an antibiotic in pre-clinical development that inhibits the bacterial DNA-dependent RNA polymerase. Previous studies showed CorA to be effective against the causative agents of sexually transmitted infections including chlamydia (*Chlamydia trachomatis*) and gonorrhea (*Neisseria gonorrhoeae*) as well as filarial infections via depletion of their essential *Wolbachia* endosymbionts. Standard in vitro toxicity tests have not raised any relevant safety concerns and support the development of CorA for use in humans. In vivo non-GLP toxicity studies in rats and dogs (maximum tolerated dose, single- and repeated dose studies) were recently completed and showed CorA to be well tolerated within the clinically relevant range (NOEL in dogs 150 mg/kg, predicted human NOEL 83.3 mg/kg).

Due to the low bioavailability of neat CorA, two amorphous solid dispersion (ASD) formulations were developed. The formulations significantly improved oral bioavailability and compound stability. Pharmacologic analysis of CorA levels in organs revealed that oral administration of the ASD formulations led to accumulation of CorA in the tibia of mice, indicating that CorA may be used as a novel antibiotic for osteomyelitis. Efficacy studies with the rodent parasite *Litomosoides sigmodontis* with the orally administered ASD formulation achieved similar reduction of *Wolbachia* as the previously published intraperitoneal injections. Lastly, we demonstrated depletion of *Wolbachia* and macrofilaricidal activity against male worms of *Onchocerca ochengi*, a close relative of the human infectious agent *Onchocerca volvulus*. Overall, our data support the continued development of CorA with phase I clinical trials planned for 2025/2026.

P2

Substrate specificity of the unique trypanosome mRNA decapping enzyme

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The trypanosome mRNA decapping enzyme ALPH1 is a promising drug target, as it is unique to Kinetoplastida. ALPH1 consists of a catalytic domain that is flanked by an unstructured, nonessential N-terminal domain and a structured and more conserved C-terminal domain that mediates interactions with other ALPH1 complex members. Here, we set out to characterize the activity of the enzyme towards a variety of substrates, combining three different types of in vitro decapping assays. We find that ALPH1 cleaves mRNA substrates independent on nucleotide sequence and cap type. Moreover, ALPH1 cleaves the pyrophosphate bond of both methylated and nonmethylated cap analogues, but, interestingly, at different phosphate positions. Finally, we found that the catalytic domain of ALPH1 is sufficient for ALPH1 activity. The biological relevance of these findings and future directions will be discussed.

P3

Analysis of the antipathogenic potential of rocaglates and their targets in *Schistosoma mansoni*

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Infection with *Schistosoma mansoni* causes schistosomiasis, which since decades is treated with a single drug – Praziquantel. The justified fear of resistance development encourages the search for new targets and drugs. It was shown that inhibition of the eukaryotic translation initiation factor 4A (eIF4A) by rocaglates has antipathogenic potential [1]. For further analysis, one potentially sensitive eIF4A isoform of *S. mansoni* was recombinantly expressed in *Escherichia coli* and purified by affinity chromatography. Thermal shift assays (TSA) were performed to investigate the potential binding of rocaglates to this isoform. Additionally, antischistosomal effects of two rocaglates (silvestrol and zotatifin) were analyzed in vitro by treating adult *S. mansoni* daily with 200 nM silvestrol or 700 nM zotatifin for seven days. To evaluate treatment effects, vitality parameters, stem-cell proliferation, and the egg-hatching rate were examined.

TSA revealed shifts of about 7°C and 9°C, respectively, thus confirming that SmeIF4A is a target of zotatifin and silvestrol. Treatment of adult worms exhibited reduced attachment ability and motility. Also, stem-cell proliferation was impaired, as demonstrated by reduced numbers of EdU+ cells. Rocaglate treatment finally reduced the egg-hatching rate in vitro, indicating that embryogenesis is compromised by inhibition of schistosomal eIF4A.

Our results demonstrate the antischistosomal potential of silvestrol and zotatifin, which may open new perspectives for drug development.

[1] Obermann, W. et al. 2023. Sci Rep. 13(1), 9297.

P4

Structure-function studies of the mRNA decapping enzyme of *Trypanosoma brucei*

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mRNA decapping in Trypanosomatids is uniquely done by the enzyme ALPH1 belonging to the ApaH family of phosphatases, unlike the Dcp2 Nudix hydrolase employed by all other eukaryotes. ALPH1 thus mechanistically differs from Dcp2 in the cap cleavage mechanism, which can be exploited for trypanocidal drug development and novel biotechnology applications. Here, we established a robust protein production protocol for *Trypanosoma brucei* ALPH1 and various truncated versions of it, consisting of bacterial expression and multi-step purification. Our SEC-MALS analyses indicate that ALPH1 is a homodimer which oligomerizes via its C-terminal domain. We established a one-step ALPH1 enzymatic activity assay using the direct fluorescent probe m7GTP-pyrene that emits an increased fluorescence signal upon cleavage, and demonstrated ALPH1 inhibition by a non-cleavable cap analog. We are in the process of engineering and screening further construct variants of the ALPH1 catalytic domain for crystallization trials. The crystal structure of ALPH1 in a complex with cap analogs and inhibitors might will further elucidate its reaction mechanism and substrate specificity, which will support our drug development efforts.

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P5

Investigation of the malate dismutation pathway as a potential drug target in *Echinococcus multilocularis*

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The zoonosis alveolar echinococcosis (AE) is caused by the metacestode of the fox tapeworm *Echinococcus multilocularis*. AE is characterized by tumor-like growth of metacestodes primarily in the liver, which is deadly if untreated. Current drug treatment is based on benzimidazoles. However, this does not lead to a cure, as benzimidazoles act only parasitostatically. Thus, novel drug treatments are needed.

Previous studies found significant release of succinate/acetate from in vitro cultured metacestode vesicles, suggesting an active malate dismutation (MD) as in other parasitic helminths. MD is a mitochondrial pathway, which generates ATP under hypoxia. It uses an alternative electron transport chain and the unusual electron carrier rhodoquinone that is absent in mammals. Thus, MD may offer an intervention point for future treatment of AE.

To investigate MD in *E. multilocularis*, we have performed metabolomic and transcriptomic analyses of in vitro cultured parasites under different oxygen conditions. We found a high increase of succinate when cultured under hypoxia/anoxia and increased expression of genes involved in rhodoquinone synthesis. Amongst them, *coq-2* showed the highest increase in expression. Coq-2 is a key enzyme in ubiquinone and rhodoquinone synthesis, but in *E. multilocularis*, only the rhodoquinone-specific isoform (described in *C. elegans*) is present. Thus, MD might be the main route for energy production under hypoxia/anoxia in *E. multilocularis*. Further experiments will investigate the essentiality of MD for parasite survival and its druggability.

P6

Response to alveolar echinococcosis: Screening of the MMV Pandemic Response Box revealed a novel promising compound

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The metacestode stage of *Echinococcus multilocularis* causes the emerging zoonotic disease alveolar echinococcosis (AE). Existing drug treatment-based interventions only exhibit a parasitostatic effect, inhibiting metacestode growth and infiltration without achieving parasite eradication. Thus, there is urgent demand for novel treating options against AE.

In this project, we employed whole organism-based screening to test the 400 compounds of the Medicines for Malaria Venture (MMV) Pandemic Response Box on *E. multilocularis* in vitro. Damage-marker release assay in combination with metacestode viability testing hereby identified 37 potentially active substances in a first screen. Confirmation screening narrowed down this selection to five efficacious compounds: alexidine, carbendazim, 2,4-diiodoemodin, ESI-09 and oxfendazole. These five hits were further characterized by assessing parasiticidal potential on *E. multilocularis* primary culture cells versus cytotoxicity on mammalian cells. ESI-09 hereby demonstrated the broadest therapeutic window outcompeting the other compounds, which displayed high mammalian cytotoxicity or lack of parasiticidal activity.

Thus, the most promising hit of this screening project against AE is the antibacterial ESI-09, an EPAC (exchange proteins directly activated by cAMP) specific inhibitor. Its mode of action in *E. multilocularis* is part of ongoing investigations and first results will be ready by the conference. Translation of these promising in vitro results into the in vivo mouse model will reveal the true potential of ESI-09 against AE.

P7

Targeting a unique mRNA decapping enzyme for trypanosomatid infectious disease drug discovery

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Trypanosomatids encode no homologues of canonical decapping enzymes, but employ the ApaHlike phosphatase ALPH1, belonging to a phosphatase family absent in mammalian systems, for the essential process of mRNA decapping. Based on thorough characterisation of ALPH1, both biochemically and in the cellular context, we conclude that ALPH1 is meeting key criteria of a robust drug target. We set out to conduct a screening campaign to identify inhibitors with the potential to become highly selective candidate drugs for trypanosomatid caused diseases, including African sleeping sickness, Chagas disease and the leishmaniases. We have developed a robust luminescent assay to monitor ALPH1 activity for high throughput screening of inhibitors, relying on the quantification of ADP liberated from a dinucleotide cap analog by a coupled enzymatic assay. Specifically, liberated ADP is first converted into ATP by pyruvate kinase, fuelling the generation of a luminescent signal by luciferin/luciferase. Inhibitors identified in primary screens are tested for interference with ADP detection by a direct assay of ALPH1 decapping activity, to rule out false positives from inhibition of the coupled enzymatic reaction. This secondary screen relies on a m7GTP-pyrene probe, which readily yields fluorescence upon ALPH1 cleavage. We present data on assay development and discuss our target-based screening approach.

P8

Activity and efficacy of the bumped kinase inhibitor BKI-1708 in vitro and in non-pregnant and pregnant toxoplasmosis and neosporosis mouse models

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Toxoplasma gondii and *Neospora caninum* are major worldwide morbidity-causing pathogens. Bumped kinase inhibitors (BKIs) – optimized to target the apicomplexan calcium-dependent protein kinase 1 (CDPK1) – proved to be safe and highly active in vitro and in vivo against several apicomplexans. When applied in vitro concomitantly to infection, BKI-1708 exhibits IC50 values in the nanomolar range - 120nM for *T. gondii* and 480nM for *N. caninum* - and does not affect HFF at concentrations up to 20 µM. Electron microscopy and immunofluorescence established that exposure of tachyzoite-infected cells to 2,5 µM BKI-1708 in vitro induces the formation of multinucleated schizont-like complexes (MNC) - characterized by continued nuclear division and enclosing intracellular zoites lacking the outer plasma membrane, unable to finalize cytokinesis. Zebrafish (*Danio rerio*) embryos treated during the first 96h following egg hatching showed that BKI-1708 did not affect early embryo development at concentrations up to 2 µM. Treatments of mice with BKI-1708 at 20 mg/kg/day during five consecutive days established an average plasma level concentration bellow 2 µM, ranging from 0.14µM to 4.95µM. Efficacy was evaluated by treatment at 20 mg/kg/day from day 9 - 13 of pregnancy in mice experimentally infected with *N. caninum* (NcSpain-7) tachyzoites or *T. gondii* (TgShSp1) oocysts. This resulted in significantly decreased cerebral parasite loads and reduced vertical transmission in both models without drug-induced pregnancy interference. BKI-1708 is highly efficacious and pregnancy-safe in these mouse models, and certainly suitable for further trials.

P9

Niclosamide ethanolamine against the fox tapeworm, *Echinococcus multilocularis*

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The fox tapeworm, *Echinococcus multilocularis*, is the most important foodborne parasite in Europe. It causes the severe disease alveolar echinococcosis (AE) in humans and other animals. The tumor-like growth of this parasite is caused by the larval metacestode stage mainly in the liver of patients. Drug treatment options are based on benzimidazoles, which are not always efficacious and can induce adverse effects. The discovery of new and better drug treatment options against AE is urgently needed.

We previously have identified the compound MMV665807 to be highly efficacious against *E. multilocularis* in vitro [1]. MMV665807 is related to niclosamide, which is used as an anthelmintic drug, but it does not reach the tissue-dwelling metacestode in the liver, as it is poorly absorbed from the intestine. We here repurposed niclosamide ethanolamine (NEN) from the field of cancer research, as it shows an improved systemic exposure profile with higher drug levels also in the liver. The activities of niclosamide and NEN in vitro on *E. multilocularis* metacestode vesicles (EC50<0.2µM) and primary parasite cells (EC50<0.3µM) with both drugs equally active. Expected liver values in mice treated with NEN are at 1-2.5 µM. Therefore, we currently follow NEN in in vivo studies in mice with AE.

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P10

Identification of anti-schistosomal starting points within Merck KGaA's Open Innovation Initiatives

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Schistosoma mansoni is a parasitic trematode that contributes to the infectious human disease schistosomiasis, which affects in excess of 240 million people worldwide. A single chemotherapeutic agent, praziquantel (PZQ), is currently used for the control of this disease. However, PZQ is ineffective against juvenile worms, necessitating repeated treatment and raising concerns around the development of resistance.

As part of open innovation initiatives with Merck KGaA, we screened two compound collections containing small molecules with drug-like properties: the 'Open Global health library' (250 compounds) and the 'Mini Library' (80 compounds), using 'Roboworm', a custom-built, automated high-content imaging platform that enables the objective repositioning of existing drugs and the identification of new compounds as next generation anthelmintics.

Across both libraries, we identified 33 compounds as hits (10% hit rate) on larval stage schistosomula. These hits were subsequently screened against adult worms. From the 33 anti-schistosomula hits, 6 compounds were identified that impacted adult worm motility; one was un-blinded as PZQ, one was identified as a Cdc25a inhibitor and four were identified as chemically related lipid-kinase inhibitors. These lipid-kinase inhibitors are currently undergoing further characterisation and validation.

Collectively, these data demonstrate the power of open innovation initiatives where Industry and academia can come together to collaborate and identify new chemical starting points for the development of next generation anti-schistosomal agents.

P11

Tools for investigation of drug resistance and screening of new compounds in the liver fluke *Fasciola hepatica*

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Triclabendazole is the most effective drug to treat *Fasciola hepatica*, a trematode parasite that infects the liver of humans and animals. However, triclabendazole resistant parasites have become increasingly prevalent with the resistance-mechanisms still unknown. We are currently establishing tools to allow testing of parasites for drug resistance and screening of compounds for fasciolicidal activity.

The methodology includes ex vivo testing of adult parasites from ruminant livers condemned at the abattoir, and the production of metacercariae / juvenile flukes via infection of the intermediate snail host.

So far, sample collections have yielded 8-60 adult *F. hepatica* per infected liver. Parasites kept their motility for up to 7 days in vitro and large numbers of eggs could be recovered during the first 24 hours of culture. We established breeding and clonal infection of the intermediate snail host *Galba truncatula* with infection rates of 60-70% and 4 to 252 metacercariae / snail produced in the first 50 days of infection. We are subsequently excysting these metacercariae and generating juvenile flukes to implement automated viability read-outs for quantification of drug sensitivities in vitro.

These tools will be used to measure triclabendazole sensitivities of *F. hepatica* field isolates, with the aim to perform subsequent population genomic studies on isolates with different phenotypes. Further, the methodology will facilitate drug screening for future drug discovery projects.

P12

Glycolysis is not a suitable pathway for identifying anthelmintic targets in *C. elegans* under standard growth conditions

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Phosphoglycerate kinase (PGK) presents an opportune drug discovery target, being essential in glycolysis for nearly all organisms. PGK has been proposed as an anthelmintic target previously [1]. Surprisingly, large-scale RNAi studies in C. elegans have not found any phenotype following pgk-1 RNAi [2-4], despite a 7.9 fold knockdown in pgk transcript level [5], which may be a result of PGK not being a rate-limiting step or incomplete knockdown. There has been identified a *C. elegans* strain that is homozygous for a mutant PGK. This mutant PGK has a large in-frame deletion including part of its active site. We have shown that this protein cannot fold when expressed in vitro by *E. coli*.

The *C. elegans* mutant strain is capable of survival under normal lab conditions with no ill effects. However, when exposed to anoxic conditions, its ability to survive relative to wild-type N2 *C. elegans* is severely diminished. This indicates that glycolysis is not an essential pathway for normal growth and survival under standard aerobic conditions and opposes traditional views on the suitability of glycolytic targets for anthelmintic discovery. This mutant PGK provides a warning against the presence of a target in an 'essential' pathway as a key selection factor without direct genetic validation in a model or parasitic nematode and testing for effects under different conditions.

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P13

How do seaweed bioactive compounds kill parasitic worms?

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Gastrointestinal parasite infections severely limit sustainable livestock production, with resistance to synthetic drugs compromising ongoing prophylactic treatments. Leveraging natural anti-parasitic agents like seaweed-derived polyunsaturated fatty acids (PUFAs) could be a viable alternative. Al- though the anti-parasitic effects of PUFAs in vitro are documented, their anthelmintic mechanisms remain unknown. This study investigates the interaction between three PUFAs- alpha-linolenic (ALA) acid, linoleic acid (LA) and eicosapentaenoic (EPA) with nematode parasites. Furthermore, transcriptomics and functional biochemical experiments will elucidate the biological pathways perturbed in nematodes after exposure to sub-lethal doses of PUFAs in-vitro. Preliminary data showed that ALA is the most toxic PUFA to Caenorhabditis elegans, with IC50 values of 48 µM and 80 µM in egg hatch and larval mortality assays, respectively. The scanning electron microscope images showed alterations in the ultrastructures of all stages of *C. elegans*, with white nodular structures appearing on the surface of embryonated eggs and worms in response to ALA exposure. Similarly, exposure of *A. suum* L3 larvae to ALA induced physical damage and puncture holes in the worm cuticle. It is envisioned that further research will provide deeper insights into the antiparasitic mechanisms of PUFAs, thereby enhancing the application of PUFA-rich plants and algae in sustainable pasture-based livestock production practices.

P14

Hippo and *Echinococcus* growth control

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The metacestode larva of the fox tapeworm *Echinococcus multilocularis* is the causative agent of the Alveolar echinococcosis (AE), a lethal zoonosis prevalent in the Northern Hemisphere. Metacestode growth within host organs is driven by pluripotent parasite stem cells and almost unlimited, leading to large tumor-like lesions. Metazoan organ size is typically controlled by the Hippo signaling pathway, but its role in *Echinococcus* development has not been studied so far. We identified and characterized *Echinococcus* Hippo pathway components by bioinformatic methodology and studied their role in parasite biology using specific inhibitors on parasite culture systems.

We identified orthologs of all canonical Hippo pathway components (e.g. the kinases Hippo and Warts as well as the co-activator Yorkie) in *Echinococcus* and demonstrated their expression in parasite larvae by in situ hybridization. Application of known Hippo pathway inhibitors targeting the Hippo pathway led to prominent, reproducible phenotypes such as multinuclear “giant cells” (XMU-MP-1 agaisnt Hippo) or massive lesions in metacestode tissue and defects in protoscolex formation (TRULI against Warts). Furthermore, inhibition of *yorkie* by RNA interference resulted in metacestode development defects.

In conclusion, this study demonstrates that a complete Hippo signaling pathway is present in *E. multilocularis*. Our data indicate that Hippo signaling contributes to proliferation dynamics of germinative stem cells, which are the decisive cell type in parasite growth within the host. These data are relevant for understanding *Echinococcus* stem cell based developmental processes and introduce Hippo signaling as a promising target pathway for the development of novel drugs against AE.

P15

Establishing State-of-the-Art infrastructure for arthropod repellent discovery

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Despite a 5% annual growth of the insect repellent market, diversity of available repellents remains limited. We have established a screening pipeline aimed at discovering novel repellents against arthropod pest species. Employing machine learning strategies as delineated by Vlot et al. (2023) [1], we pre-screened approximately 500 candidate compounds using the malaria vector *Anopheles stephensi*. A total of 90 compounds were screened further against a baseline panel of species: ticks (*Ixodes ricinus*), cat fleas (*Ctenocephalides felis*), bed bugs (*Cimex lectularius*), and body lice (*Pediculus humanus humanus*). The most promising test substances are further evaluated against an expanded panel, including additional tick species (genera *Dermacentor, Rhipicephalus, Hyalomma*), clothes moths (*Tineola bisselliella*), and house dust mites (*Dermatophagoides pteronyssinus*). Customised test systems have been developed for each species. We report on the promising first results of the baseline panel. A surprisingly high percentage of the compounds exhibited levels of repellency equal or superior to DEET, and many were effective across multiple test species, confirming the effectiveness of our approach. We are confident that the continued development and validation of these compounds will lead to the introduction of innovative repellents to the market, providing new solutions for arthropod control and protection.

[1] Marnix Vlot, Martijn Vos, Rob Henderson, Luuk Berning, Koen Dechering (2023): Use of machine learning to identify novel mosquito repellents. Abstract DDDS 2023.

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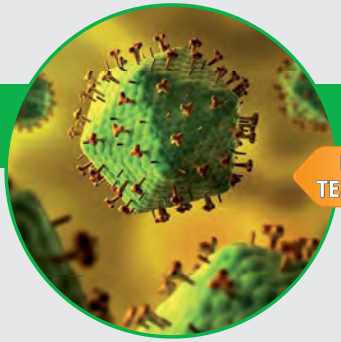

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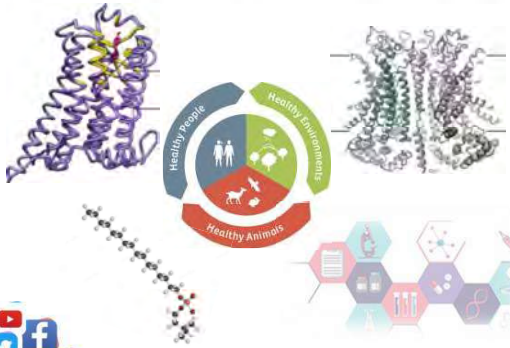

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