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für Parasitologie

Joint meeting of the
26th Drug Design & Development Seminar (DDDS) 2026
of the German Society for Parasitology (DGP)
&
The European Cost Action – CA21111 – "OneHealthdrugs"

"Human and Animal Parasitic Diseases – Bridging the Innovation Gap"

March 17th – 20th, 2026

Giessen, Germany

Cover legend, from left to right:

In vitro cultured metacestodes of *Echinococcus multilocularis* (Britta Lundström-Stadelmann, Institute of Parasitology, Bern, CH)

Hatching tick larva (Bastian Gerst, Freie Universität Berlin, DE)

Toxoplasma tachyzoites with mitochondria marker in pink, nuclear pore marker in light blue, and DAPI in purple (Lilach Sheiner, University of Glasgow, UK)

Immature liver fluke after treatment with a $TRPM_{PZQ}$ agonist (Simone Häberlein, Institute of Parasitology, Giessen, DE)

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Conference website: https://eveeno.com/ddds2026

We gratefully acknowledge the financial support of our sponsors and donors:

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 (Eberhard Karls University Tübingen, 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 stimulate One-Health approaches to combat parasitic diseases.

The main topics include but are not limited to:

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

About the Cost Action CA21111 / OneHealthdrugs

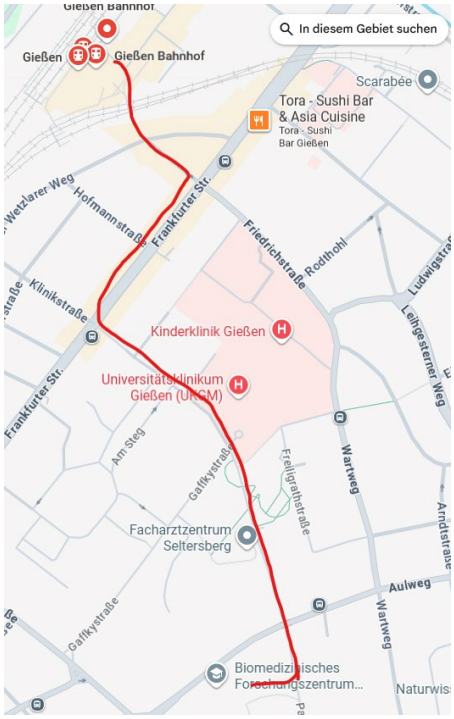
OneHealthdrugs aims to coordinate the discovery of drugs that stop vector-borne infections in both human and veterinary settings according to the principles of the optimal profile for both organisms, increasing quality and reducing environmental impact. The COST Action is a platform aiming at the integration and generation of synergies among drug R&D experts from the chemical / biological / human / veterinary and earth science within academies, SMEs, industries, governments. The platform encompasses pre-clinical drug discovery, animal studies, and drug delivery. Strategies such as bioinformatics, PROTACs, nanotechnology will be enhanced. OneHealthdrugs impacts in Europe and in disease-endemic countries. The action provides a compound database and a white chart about the discovery of new drugs for human and animal infections.

Venue

Biomedizinisches Forschungszentrum Seltersberg (BFS)
Schubertstraße 81
35392 Gießen

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

How to get there



By train:

Leave the main station (BHF), turn right, go up the (stone) stairs, cross the pedestrian bridge, go straight ahead to the intersection Frankfurter Strasse, turn right into Frankfurter Strasse, go to the crossing Klinikstraße, turn left into Klinikstraße, go straight ahead to Paul-Meimberg-Straße (which leads along under a bridge, below Aulweg). Behind the bridge turn right, to enter the BFS, which is the most colourful building you will see (see marked route, ~1.6 km).
See also: https://www.uni-giessen.de/en/faculties/bfs/howfindus?set_language=en

Here you find more information about buses in Giessen:
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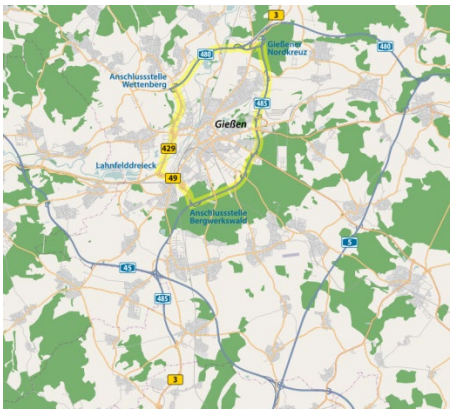

By car:

Gießen is surrounded by the highways A480 and A485. These highways are connected to the highways A5 and A45.
Coming from the Gießener Ring (A485), take exit Bergwerkswald, Uniklinikum into town, at the first traffic light, turn right into Robert-Sommer-Straße, go straight ahead to the end of the street, turn right into Schubertstraße. The colorful building BFS is located at the next corner Schubertstraße, Aulweg.
Car parking is chargeable close to the BFS or for free in 5-10 min walking distance (streets: Schlangenzahl and Carl-Franz-Straße), if you find a free space.

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Life forward

Tuesday, 17.03.2026		
17:00	**20:00**	**Registration & Poster set-up – BFS Conference Venue, Giessen**
18:00	**20:00**	**Welcome Reception at the BFS Conference Venue, Giessen**

Wednesday, 18.03.2026			Speaker	Title	Institution
8:00	**9:00**	**Registration & Poster set-up**			
9:00	**9:20**	**Welcome & Introduction**	**Christoph Grevelding, Simone Häberlein, Franco Falcone, Maria Paola Costi, Sandra Noack, Paul M. Selzer Stefan Arnhold, Dean of the Faculty of Veterinary Medicine, JLU Giessen**		
9:20	**10:00**	Keynote	Ard Nijhof	Artificial tick feeding: opportunities, limitations, and perspectives	Freie Universität Berlin, Germany
10:00	**10:20**	Session Chair: Ronald Kaminsky	Maxime Madder	Evaluation of Nitisinone (NTBC) as a systemic ectoparasiticide against blood-feeding arthropods: *in vitro* and *in vivo* studies	Clinglobal, Mauritius
10:20	**10:40**		Koen Dechering	4-hydroxyphenylpyruvate dioxygenase is a validated acaracide target for control of one host ticks	TropIQ Health Sciences, The Netherlands
10:40	**11:10**	**Coffee break**			
11:10	**11:50**	Keynote	Guy Caljon	Advancing the battle against kinetoplastid diseases: Finetuning models for One Health drug discovery	University of Antwerp, Belgium
11:50	**12:10**	Session Chair: Anabela Cordeiro-da-Silva	Sarah Hendrickx	From mouse to the patient: Building predictive leishmaniasis models for efficient drug discovery with a “fail fast and cheap” principle	University of Antwerp, Belgium
12:10	**12:30**		Maria Paola Costi	One Health science and technology in the development of safer antiparasitic drugs	University of Modena and Reggio Emilia, Italy
12:30	**12:50**		Ronald Kaminsky	Balancing benefits and hazards of antiparasitics in a changing ecological landscape	ParaConsulting, Germany
12:50	**14:10**	**Lunch break**			
14:10	**14:50**	Keynote	Lilach Sheiner	Structure-function and inhibition of *Toxoplasma gondii* respiratory chain complex III and supercomplex III_2IV	University of Glasgow, UK
14:50	**15:10**	Session Chair: Anja Taubert	Wesley van Voorhis	Bumped kinase inhibitors for calf cryptosporidiosis and sheep toxoplasmosis	University of Washington, USA
15:10	**15:30**		Walter Bronkhorst	Searching for novel anti-malarials using target based drug discovery: SHMT as novel target in malaria drug discovery	TropIQ Health Sciences, The Netherlands
15:30	**15:50**		Ross Douglas	Unique actin-like proteins Alp1 and Alp2b are essential for *Plasmodium* motility and malaria transmission	Justus Liebig University Giessen, Germany
15:50	**16:20**	**Coffee break**			

16:20	**16:40**	Session Chair: Friederike Knapp-Lawitzke	Thomas J. Schmidt	Aminosteroids from Buxaceae and Apocynaceae as leads to new antiprotozoal drugs: Structural diversity and structure-activity relationships	University of Münster, Germany
16:40	**17:00**		Theodora Calogeropoulou	Design, synthesis and evaluation of antiparasitic activity of new heterocyclic phosphomimetic derivatives	National Hellenic Research Foundation, Greece
17:00	**17:20**		David Magri	Ferrocene *Cinchona* alkaloid copolymers as anti-parasitic and fluorescence imaging tools	University of Malta, Malta
17:20	**19:00**	**Poster session & evaluation with snacks and drinks**			

Thursday, 19.03.2026			**Speaker**	**Title**	**Institution**
9:00	**9:40**	Keynote	Natacha Gaillard & Ashwani Sharma	Building precision antiparasitics through rational drug design: The ParaX® platform	ASTRA Therapeutics, Switzerland
9:40	**10:00**	Session Chair: Christian Epe	André Lopes	Synthesis and antileishmanial activity of 8-aminophenyl-pyrimidopyrimidine-based compounds	University of Minho, Portugal
10:00	**10:20**		Harry De Koning	Drug action, drug resistance and drug targeting in animal trypanosomiasis	University of Glasgow, UK
10:20	**10:40**		Joachim Kloehn	Novel fosmidomycin analogues with improved bioavailability to target *Toxoplasma gondii*	University of Geneva, Switzerland
10:40	**11:10**	**Coffee break**			
11:10	**11:50**	Keynote	Mostafa Zamanian	Advancing anthelmintic discovery through parallel tracks of target identification and phenotypic screening	University of Wisconsin-Madison, USA
11:50	**12:10**	Session Chair: Marc Hübner	Hala Fahs	A high-throughput anthelmintic screening pipeline uncovers novel and repurposed anthelmintics targeting filarial and intestinal parasites	New York University, United Arab Emirates
12:10	**12:30**		Marius Spohn	Strategic collaboration to develop ecologically sustainable antiparasitic solutions from microbial natural products	Fraunhofer IME, Giessen, Germany
12:30	**12:50**		Felix Mühlemeyer	Strevertene A, a Streptomyces-derived macrolide with selective activity against the human parasite *Schistosoma mansoni*	Fraunhofer IME, Giessen, Germany
12:50	**14:20**	**Group photo & Lunch break**			
14:20	**15:00**	Keynote	Britta Lundström-Stadelmann	The metabolism of *Echinococcus* and novel targets for treatment of echinococcosis	University of Bern, Switzerland
15:00	**15:20**	Session Chair: Richard Marhöfer	Maria Eugenia Ancarola	Succinate dehydrogenase activity in helminths is inhibited *in vitro* by triclabendazole and its metabolites	University of Bern, Switzerland
15:20	**15:40**		Pascal Zumstein	Identification and characterization of cMDH as a putative drug target in alveolar echinococcosis	University of Bern, Switzerland

15:40	**16:00**		Simone Häberlein	From omics to targets to drugs: strategies to fight liver flukes	Justus Liebig University Giessen, Germany
16:00	**16:30**	**Coffee break**			
16:30	**16:50**	Session Chair: Maria-João Ribeiro Peixoto de Queiroz	Gaelle Lentini	Dual proteomic and chemical-genetic evidence identifies proteases as druggable drivers of *Trypanosoma cruzi* egress	University of Bern, Switzerland
16:50	**17:10**		Daniel Sojka	Multi-target drug discovery against *Babesia divergens:* targeting invasion, egress, and proteostasis	Biology Centre CAS, Czech Republic
17:10	**17:30**		Martin Blume	Classic metabolic vulnerabilities in dormant and pan drug-tolerant *Toxoplasma gondii* tissue cysts revealed by drug screening, proteomic and metabolomic analysis	Robert Koch-Institute, Germany
18:00	**23:00**	**Bus transfer (return) to conference dinner venue Conference dinner & network session with „Dribbdeblues“**			

Friday, 20.03.2026			**Speaker**	**Title**	**Institution**
9:00	**9:40**	Keynote	Makedonka Mitreva	GPCR antagonists with potent *in vitro* and *in vivo* macrofilaricidal activity	Washington University School of Medicine, USA
9:40	**10:00**	Session Chair: Hala Fahs	Denis Voronin	Dual mechanisms of niclosamide in targeting the *Wolbachia*-filarial worm symbiosis	Systems Genomic Section, LPD, NIAID, NIH, USA
10:00	**10:20**		Manfred Jung	Chemical probes to study the role of the lysine demethylase LSD1 in *Leishmania* infection	University of Freiburg, Germany
10:20	**10:40**		Biljana Arsić	Drug repurposing for kala-azar, malaria and toxoplasmosis potential treatments	University of Niš, Serbia
10:40	**11:10**	**Coffee break**			
11:10	**11:50**	Keynote	Arnold Grünweller	The RNA helicase eIF4A as a target for the development of pan-antivirals and anti-pathogenic drugs – From natural compounds to new eIF4A inhibitors	Philipps University Marburg, Germany
11:50	**12:10**	Session Chair: Sébastien Pomel	Sophie Welsch	Evaluation of the RNA helicase eIF4A as potential drug target in *Schistosoma mansoni* and its inhibition by rocaglates and pateamines	Justus Liebig University Giessen, Germany
12:10	**12:30**		Frederic Risch	Repurposing of fosfomycin for filarial infections	University Hospital Bonn, Germany
12:30	**12:50**		Raffi Aroian	Combination-based Cry-based anthelmintic therapies	UMASS Chan Medical School, USA
12:50	**13:15**	**Awards session Wrap-up & Closing**		**Simone Häberlein, Paul M. Selzer**	
		Boxed lunch			

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Poster	Name	Title	Institution
P1	Hamed Eid A. Alkhalaf	Towards nucleoside analogues with potent activity against *Trypanosoma* and *Leishmania* species	University of Glasgow, UK
P2	Maria-João R. P. Queiroz	Synthesis of (hetero)aryl and alkylaminothieno[2,3-b]pyridines, antiparasitic evaluation and SARs studies	Universidade do Minho, Portugal
P3	Sébastien Pomel	Evaluation of antileishmanial and antimalarial activities of endoperoxide analogs derived from marine natural products	Université Paris-Saclay, France
P4	Caroline Busse	Unique actin-like proteins 3 and 5a are essential for *Plasmodium* oocyst formation and development	Justus Liebig University Giessen, Germany
P5	Eliska Drncova	Mitochondrially targeted iron chelators as a potential pharmaceutical for protozoan parasites and pathogenic yeast	Charles University, Czech Republic
P6	Hafidh Akkari	The use of medicinal plants against vector-borne diseases: Evaluation of *in vitro* leishmanicidal activity of the Chamomile essential oil	University of Manouba, Tunisia
P7	Razieh Tavakoli Oliaae	The potential role of nicotinamide on *Leishmania tropica*: An assessment of inhibitory effects, cytokine gene expression and arginase profiling	Justus Liebig University Giessen, Germany
P8	Hannah Wegner	Vaccine adjuvants can boost oxfendazole efficacy in the *Litomosoides sigmodontis* filarial rodent model	University Hospital Bonn, Germany
P9	Essia Sebai	Exploring *Myrtus communis* as a plant-based anthelmintic for *Haemonchus contortus* and *Heligmosomoides polygyrus*	National School of Veterinary Medicine of Sidi Thabet, Tunisia
P10	Hasanuzzaman Talukder	Tannin-free natural products modulate serotonergic, dopaminergic and tubulin associated pathways in *Caenorhabditis elegans* to reveal novel anthelmintic drug targets	Bangladesh Agricultural University, Bangladesh
P11	Archile Paguem	Ethno-pharmacology and anthelminthic bioactivity of plants used in traditional medicine in Cameroon	Justus Liebig University Giessen, Germany
P12	Julio López-Abán	Standardization of culture techniques and evaluation of compounds against *Fasciola hepatica*	Universidad de Salamanca, Spain
P13	Alice Bernal	A new automated, motility-based screening assay for discovery of compounds with activity against the juvenile stage of *Fasciola hepatica*	University of Bern, Switzerland
P14	Erik Wotschel	Molecular characterization and therapeutic potential of the transcription factor HNF4 in the liver fluke *Fasciola hepatica*	Justus Liebig University Giessen, Germany
P15	María Alejandra Villamizar Monsalve	*In vivo* efficacy of tubulin inhibitors against *Schistosoma mansoni*	Universidad de Salamanca, Spain
P16	Saranya Geetha	Pairing-dependently expressed GPCRs as novel therapeutic targets in *Schistosoma mansoni*	Justus Liebig University Giessen, Germany
P17	Ibukun Busari	Natural product-driven anthelmintic discovery: antinematode activity and drug-development prospects of *Terminalia glaucescens* against *Haemonchus contortus*	The University of Salford, UK

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Keynote Talk

Artificial tick feeding: Opportunities, limitations, and perspectives

Ard M. Nijhof [1, 2]

[1] Institute for Parasitology and Tropical Veterinary Medicine, Freie Universität Berlin, Robert-von-Ostertag-Str. 7, 14163, Berlin, Germany

[2] Veterinary Center for Resistance Research, Freie Universität Berlin, Robert-von-Ostertag-Str. 8, 14163, Berlin, Germany

E-mail: ard.nijhof@fu-berlin.de

Artificial feeding systems have become important tools for the study of hematophagous arthropods, vector competence, and the maintenance of laboratory colonies, while also contributing to the reduction of animal use in ectoparasiticide research. These systems typically combine an artificial membrane, a blood meal, and controlled environmental conditions to mimic natural feeding while enabling precise experimental manipulation. Although artificial feeding has been successfully established and optimized for an increasing number of blood-feeding arthropods, ixodid ticks remain particularly challenging due to their prolonged feeding periods and complex feeding requirements.

Despite these constraints, artificial tick feeding systems, particularly membrane-based approaches employing silicone membranes and host-derived stimuli, offer potential for acaricide discovery. They allow controlled exposure of ticks to defined concentrations of candidate compounds, supporting the in vitro assessment of mortality, feeding inhibition, and reproductive effects. Artificial feeding approaches have been used to evaluate systemic acaricides and to provide comparative efficacy data that can support early-stage compound selection.

While still technically demanding and laborious, and inherently low throughput, artificial tick feeding may provide a valuable bridge between *in vitro* screening and *in vivo* studies and continues to evolve as a useful tool in the development of novel strategies for tick control.

Evaluation of nitisinone (NTBC) as a systemic ectoparasiticide against blood-feeding arthropods: *in vitro* and *in vivo* studies

M. Madder[1], J. Liebenberg[2], S. Chapin[3], K. Dechering[4], M. Vlot[4], J. Trentelman[4], J. J. Fourie[5]

[1]Clinglobal, Tamarin, Mauritius
[2]Clinvet, Bloemfontein, South Africa
[3]Clinaxel, Loos, France
[4]TropIQ Health Sciences, Nijmegen, The Netherlands
[5]Clinvet International Pty (Ltd), Waverly, United States
E-mail: maxime.madder@clinglobal.com

Nitisinone (NTBC), an inhibitor of 4-hydroxyphenylpyruvate dioxygenase (HPPD), was assessed as a systemic endectocide targeting blood-feeding arthropods using both in vitro and *in vivo* models. *In vitro* tests evaluated NTBC's lethal concentrations on engorged female *Rhipicephalus microplus*, *Rhipicephalus appendiculatus* (via topical exposure), and *Ixodes ricinus*, *Dermacentor reticulatus*, *Stomoxys calcitrans*, and *Aedes aegypti* (via systemic exposure). Topical NTBC application showed no acaricidal effect on *Rhipicephalus* spp. at up to 1000 ppm, while systemic NTBC caused high mortality, including 91.5% in *I. ricinus* (60 ppm), 70.3% in *D. reticulatus* (120 ppm), and over 90% in *A. aegypti* and *S. calcitrans,* with LC_{90} values of 0.137 ppm for both insects.

An *in vivo* study in cattle (doses: 2, 5, or 7 mg/kg) found NTBC to be well tolerated and pharmacokinetic analysis demonstrated rapid absorption ($T_{max} \approx 0.25$ h), short elimination half-life (3.5–3.8 h), and dose-proportional increases in C_{max} and AUC. Efficacy against *R. microplus* increased with dosage, reaching 40.6% reduction in engorged female tick counts at 7 mg/kg, and persistent efficacy of 35.4%. Limited activity against existing *I. ricinus* was observed, while 60-80 reduction in viability of *S. calcitrans* was seen across all doses. Overall, the data validate HPPD as a promising ectoparasiticide target. Efficient control of ticks would require an inhibitor with a longer terminal half-life.

4-hydroxyphenylpyruvate dioxygenase is a validated acaracide target for control of one host ticks

Koen Dechering[1], Marnix Vlot[1], Matěj Kučera[2], Bente van Putten-Somsen[1], Martijn Vos[1], Julian Liebenberg[3], Maxime Madder[3], Jan Perner[2], Jos Trentelman[1]

[1]TropIQ Health Sciences, Nijmegen, The Netherlands.
[2]Institute of Parasitology, Biology Centre, Czech Academy of Sciences, České Budějovice, Czech Republic
[3]Clinvet, Bloemfontein, South Africa.

4-hydroxyphenylpyruvate dioxygenase (HPPD) is an essential enzyme in blood-feeding ectoparasites. It detoxifies the excess of tyrosine ingested with a blood meal by converting tyrosine-derived 4-hydroxyphenylpyruvate into homogentisate. We characterized recombinantly expressed mosquito, tick and human HPPD orthologues and show that these can be potently inhibited by triketone and diketonitrile herbicides. Membrane feeding assays showed rapid killing of blood-feeding *Anopheles* mosquitoes but rather slow killing of *Ixodes* ticks. The lethal effects could not be rescued by supplementing the bloodmeal with homogentisate, suggesting that the toxic effects result from accumulation of metabolites upstream of HPPD. Studying different dietary conditions showed that a high protein meal is essential for killing activity of HPPD inhibitors, with highest mortality observed with hemoglobin as the main protein. Although the slow onset of killing observed in *Ixodes* ticks is not in line with acaracide target product profiles for companion animals, it is less of a concern for control of ticks that parasitize livestock. As a proof of concept, we performed a clinical trial in Friesian Holstein cattle treated with a single intravenous dose of nitisinone and challenged with *Rhipicephalus microplus* larvae. Despite a very short-lived exposure we observed a significant reduction in total adult tick counts. The combined data indicate that HPPD is a validated, selective and druggable target for control of one host ticks.

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CTO
w.bronkhorst@tropIQ.nl

Koen Dechering, PhD
VP Business development
k.dechering@tropIQ.nl

Keynote Talk

Advancing the battle against kinetoplastid diseases: Finetuning models for One Health drug discovery

Guy Caljon

Laboratory of Microbiology, Parasitology and Hygiene (LMPH), University of Antwerp, Antwerp, Belgium

E-mail: Guy.Caljon@uantwerpen.be

Kinetoplastid diseases continue to impose a substantial burden on human and animal health, with limited therapeutic options and the risk of treatment failure. While sleeping sickness caused by *Trypanosoma brucei gambiense* is targeted for elimination by 2030, animal trypanosomiasis persists as a major global constraint on livestock productivity. Leishmaniasis likewise poses serious public health challenges and includes a significant veterinary dimension. The current situation underscores the continued need of identifying novel and effective chemical entities.

The presentation will cover lessons learnt from mouse infection models that support the identification of high-quality leads. A range of first-line standard and more refined animal models, including bioluminescent infection models, enables deeper insights into parasite biology and drug action. Challenges include elimination of parasites from protected tissue niches and tackling parasites in metabolically altered, drug-tolerant states such as quiescence. In addition, the requirement of a broad-spectrum activity against multiple kinetoplastid species has triggered animal-friendly approaches to achieve the discovery of advanced leads that meet the respective target product profiles. Furthermore, as the environmental impact of new drugs becomes integral to the One Health framework, there is a growing need for ecotoxicologically relevant assays in the anti-kinetoplastid R&D pipeline. The presentation will outline emerging initiatives to address these gaps, including novel assays and drug discovery strategies towards de-risked leads and drug development candidates.

From mouse to the patient: Building predictive leishmaniasis models for efficient drug discovery with a “fail fast and cheap” principle

S. Hendrickx[1], P.B. Feijens[1], A. Matheeussen[1], M. Vleminckx[1], A. Baeza Garcia[1], F. Escudié[2], E. Chatelain[2], and G. Caljon[1]

[1] Laboratory for Microbiology, parasitology and Hygiene (LMPH, University of Antwerp, Antwerp, Belgium, [2] Drugs for Neglected Diseases initiative, Geneva, Switzerland

E-mail: sarah.hendrickx@uantwerpen.be

"Fail fast, fail cheap" is a well-known concept in drug discovery, aiming to quickly identify and abandon ineffective drug candidates early in development by investing in well-considered preclinical assays to avoid expensive late-stage failures. Over the years, our lab has significantly invested in designing predictive *in vitro* and *in vivo* models to support this strategy in leishmaniasis drug discovery. We developed a bioluminescent mouse model for *Leishmania infantum* that, in combination with a pharmacokinetic testing and *in vitro* time-to-kill assays, can be applied to predict treatment failure of novel drug leads.

The established models have been exploited to shed light on the clinical failure of fexinidazole (FEX) for visceral leishmaniasis (VL) and allopurinol for canine leishmaniasis (canL). Although a swift dose-dependent parasite clearance was observed in the bioluminescent BALB/c mouse model for FEX, complete parasite elimination was not achieved in the liver, resulting in post-treatment relapse. Pharmacokinetic analyses and *in vitro* and *in vivo* time to kill assays indicated a good systemic exposure, but a slow cidal drug action. For allopurinol a static antiparasitic effect was observed, which quickly resulted in treatment relapse after discontinuation of treatment.

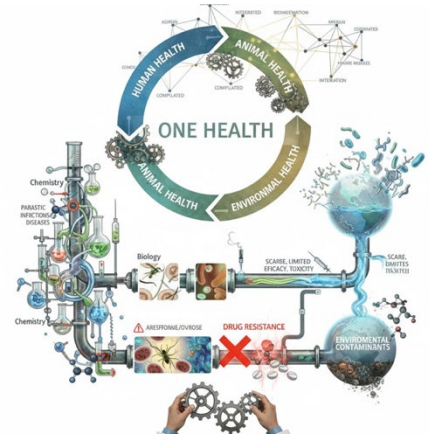
These findings highlight the benefit of the established preclinical models to understand clinical failure in VL and canL and lay the foundation for the discovery of more potent drug development candidates.

One Health science and technology in the development of safer antiparasitic drugs

Maria Paola Costi[1], Daniele Aiello[1], Lorenzo Tagliazucchi[1,2], Anabela Cordeiro[3], Sheraz Gul[4]

[1]University of Modena and Reggio Emilia, Via Campi 103, Modena, Italy [2]University of Parma Parco Area delle Scienze 27/A 43124 Parma, Italy, [3]Institute for Research and Innovation in Health, University of Porto, 4200-135, Porto, Portugal, [4]Fraunhofer Institute for Translational Medicine and Pharmacology, Schnackenburgallee 114, Hamburg, 22525, Germany.

The One Health field faces significant challenges in synchronizing multidisciplinary expertise to address global health threats. Chemistry and biology are uniquely positioned to bridge these gaps, particularly in combating antimicrobial resistance driven by the overuse of pharmaceuticals in human and veterinary medicine [1,2]. Beyond clinical efficacy, chemistry is vital for mitigating environmental contamination caused by Active Pharmaceutical Ingredients and their metabolites.



Our collaborative research focuses on transforming drug discovery by integrating ecotoxicological principles at the earliest design stages. By prioritizing "greener" chemical scaffolds today, we ensure the development of safer, environmentally friendly drugs tomorrow. This work showcases two novel methodologies: I. Cleaner Scaffold Selection. A machine learning-driven approach used to identify environmentally sustainable starting compounds for drug development [3]. II. Ecotox-Clean Target Identification: The use of Mass Spectrometry proteomics to identify protein targets in *Leishmania infantum* treated with new antiparasitic agents [4]. This effort utilizes the SeqAPASS tool to ensure targets are unique and ecotoxicologically safe. While experimental validation is ongoing, these strategies represent a significant step toward consolidating a "safer-by-design" principle. By embedding environmental safety into the drug discovery pipeline, we move closer to a truly integrated One Health approach that protects human, animal, and ecological wellbeing.

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Balancing benefits and hazards of antiparasitics in a changing ecological landscape

Ronald Kaminsky[1] and Paul M. Selzer[2]

[1]*ParaConsulting, Haeg-Ehrsberg, Germany*

[2]Eberhard Karls University Tübingen, Interfaculty Institute of Biochemistry, Tübingen, Germany

Email: [1]para.c@gmx.de; [2]paul.selzer@gmx.de

Endo- and ectoparasites including helminths, protozoa, ticks, fleas, and mosquitoes pose a substantial threat to the health of humans, livestock, companion animals, and plants. Driven by medical needs for human and animal health, antiparasitic agents are widely and effectively used for treatment and prevention. However, their extensive application carries significant risks: the emergence of drug resistance and the contamination of ecosystems, with detrimental effects on non-target organisms that may contribute to the global decline in biodiversity. In response to these concerns, several antiparasitic compounds with high toxicity and environmental persistence, such as the topically applied neonicotinoid imidacloprid and the phenylpyrazole fipronil, have been banned for use in agriculture and food-producing animals in many regions of the world. Despite these restrictions, these substances remain available for the treatment of parasites in companion animals. While the ecological impact of their former agricultural use is well documented, recent studies increasingly link the ongoing use of these compounds in pets to environmental contamination, particularly of aquatic ecosystems. These findings underscore the urgent need to balance the therapeutic benefits of antiparasitic drugs with their ecological hazards. They highlight the importance of developing and deploying agents with reduced environmental activity and of integrating non-chemical strategies into parasite control and prevention programs.

Keynote Talk

Structure-function and inhibition of *Toxoplasma gondii* respiratory chain complex III and supercomplex III_2IV

Andrew E MacLean[1], Shikha Shikha[1], Mariana Ferreira Silva[1], Amit Meir[1], Michael K Riscoe[2], J Stone Doggett[2], Alexander Mühleip[3] and Lilach Sheiner[1]

[1] Glasgow Centre for Parasitology, School of Infection and Immunity, University of Glasgow, UK; [2] VA Portland Health Care System, Portland, OR, USA; [3] Institute of Biotechnology, Helsinki Institute of Life Science HiLIFE, University of Helsinki, Finland

Apicomplexan parasites cause diseases such as malaria and toxoplasmosis that affect the health of millions of people worldwide, yet the available drugs are suboptimal. Moreover, we have poor understanding of basic parasite biology. It is thus of great importance to understand apicomplexan biology and to leverage the resulting insights to inform drug discovery.

The apicomplexan mitochondrial electron transport chain (mETC), an already validated drug target, is indispensable for parasite survival and transmission. It is further distinguished from the host by a highly divergent subunit composition. Understanding how this divergence affects mETC complexes' structure, and exploring opportunities for selective inhibition that this divergence might harbour, bears high potential for exposing new mitochondrial biology and informing drug discovery.

Using complexes purified from the model parasite *Toxoplasma gondii*, cryoEM structures, we revealed how clade-specific subunits create a conserved apicomplexan mETC supercomplex interface with a distinctive kinked organization, indicating that respiratory supercomplexes likely arose independently across eukaryotic lineages. Genetic disruption that destabilizes the supercomplex demonstrate that it is crucial for overall parasite fitness.

We further examined inhibition by the antimalarial atovaquone and defined the molecular interactions that explain parasite selectivity.

Finally, we characterized the binding of ELQ-300, which is in preclinical development stage, uncovered an inverted binding pose relative to mammalian enzymes and designed new ELQ derivatives with subnanomolar potency against *T. gondii*.

Bumped kinase inhibitors for calf cryptosporidiosis and sheep toxoplasmosis

W.C. Van Voorhis[1], R. Choi[1], M.A. Hulverson[1], D.A. Schaefer[2], D.P. Betzer[2], R. Sánchez-Sánchez[3], W. Huang[4], A. Hemphill[5], S.L.M. Arnold[6], L.K. Barrett[1], T.J. Kennedy[7], K.K. Ojo[1], J.S. Doggett[8], L.M. Ortega-Mora[3], M.W. Riggs[2], E. Fan[4]

[1] Department of Medicine, CERID, University of Washington School of Medicine, Seattle, WA, USA; [2]School of Animal and Comparative Biomedical Sciences, College of Agriculture, Life and Environmental Sciences, University of Arizona, Tucson, AZ, USA; [3]SALUVET, Animal Health Department, Faculty of Veterinary Sciences, Complutense University of Madrid, Madrid, Spain; [4]Department of Biochemistry, University of Washington, Seattle, WA, USA; [5]Institute of Parasitology, Vetsuisse Faculty, University of Bern, Bern, Switzerland; [6]Department of Pharmaceutics, University of Washington School of Pharmacy, Seattle, WA, USA; [7]Eleven Bravo LLC., Westport, WI, USA; [8]Div. of Infectious Diseases, Portland VA Medical Center, Portland, OR, USA.
E-mail: wesley@uw.edu

Cryptosporidiosis and toxoplasmosis continue to burden animals and humans with serious consequences, yet therapeutics for these infections need improvement in both efficacy and safety. We developed two Bumped Kinase Inhibitors (BKIs), BKI-1708[1] and BKI-1748.[2] In *Cryptosporidium parvum*, BKI-1708 targets Calcium-Dependent Protein Kinase 1 (CDPK1) without appreciably inhibiting mammalian protein kinases [1]. In *Toxoplasma gondii*, both BKIs dually target CDPK1 and Mitogen-activated protein kinase-like 1 (MAPKL1) [2,3].

BKI-1708 clears immunosuppressed mice and newborn calves of *C. parvum* with three days of oral therapy.[1] Calf cryptosporidiosis diarrhea is largely abrogated within one day of therapy.[1] BKI-1708 is converted to the active metabolite, M2/1862, also responsible for the *C. parvum* clearance.[1] There was no toxicity in mice, rats, and dogs, even when BKI-1708 is administered at 20 times the exposure needed for efficacy [1]. Thus, BKI-1708 is a safe and efficacious preclinical lead for One-Health cryptosporidiosis therapy.

The relatively short terminal half-life and poor oral exposure of BKI-1708 in sheep reduced its usefulness, and thus BKI-1748 with superior ADME and PK has been studied for ovine congenital toxoplasmosis [2, 4]. Sheep in mid-gestation (90 days) were infected with *T. gondii* and randomized to either BKI-1748 treatment or placebo in three separate experiments. Those treated with BKI-1748 demonstrated decreased fetal loss and eliminated lamb and maternal *T. gondii* infection, even when treatment was delayed to 7 days post-infection. When treatment was further delayed to day 14 post-infection, at the time of seroconversion to anti-*T. gondii* IgM, there was still reduced fetal loss and a significant reduction in transplacental transmission [unpublished]. Therefore, BKI-1748 is a safe and effective preclinical lead for One-Health congenital toxoplasmosis therapy.

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Searching for novel anti-malarials using target based drug discovery: SHMT as novel target in malaria drug discovery

Bente van Putten-Somsen, Lisa Nooren, Marloes de Bruijni-van den Tillaart, Martijn Vos, Walter Bronkhorst

TropIQ Health Sciences, Nijmegen, The Netherlands

There is an urgent need for new, affordable, and safe anti-malarial drugs with novel modes of action. Artemisinin-based combination therapies (ACTs) have been highly effective against *Plasmodium* parasites, yet resistance to these front-line treatments is spreading at an alarming pace. To counter this threat, the development of novel anti-malarials targeting new biological pathways is essential.

At TropIQ, we apply a target-based discovery approach, selecting *Plasmodium* proteins that are essential for parasite survival and display favorable properties for small-molecule intervention. These proteins are recombinantly expressed, purified, and integrated into biochemical assays to enable systematic screening of large compound libraries.

One of our key targets is serine hydroxymethyltransferase (SHMT), a pyridoxal 5′-phosphate (PLP)-dependent enzyme central to the folate cycle. SHMT catalyzes the transfer of a one-carbon unit from serine to tetrahydrofolate, generating 5,10-methylenetetrahydrofolate and glycine—crucial intermediates for amino acid metabolism, nucleotide biosynthesis, and methylation reactions. SHMT is of particular interest because other enzymes in the folate cycle, such as dihydrofolate reductase (DHFR), have already been successfully targeted by antifolate inhibitors like pyrimethamine and cycloguanil. In addition, PfSHMT has been designated as a high-priority target for drug discovery based on a comprehensive data-mining study conducted by the Malaria Drug Accelerator (MalDA) consortium. To date, however, only limited chemical space has been explored against SHMT.

We have successfully expressed and purified SHMT from *Plasmodium falciparum* (*Pf*SHMT), *Plasmodium vivax* (*Pv*SHMT), and human (*Hs*SHMT) to enable selectivity studies. Two orthogonal biochemical assays were established and optimized to quantify the enzymatic activity of the SHMT proteins, allowing us to validate SHMT inhibition by small molecules. One of these assays was further miniaturized and fully automated in 384-well format to support high-throughput screening. To date, our lab has screened over 75,000 small molecules for SHMT inhibition, using our established assay format. Furthermore, a DNA-encoded library screen was performed in which 10^{18} compounds were screened for binding to both *Pf*SHMT and *Hs*SHMT. This parallel screening strategy has yielded selective binders for *Pf*SHMT. Hit compounds identified in both screening campaigns are now undergoing biochemical validation and parasite growth inhibition assays, laying the groundwork for extensive hit-to-lead efforts in the discovery of next-generation anti-malarials.

Unique actin-like proteins Alp1 and Alp2b are essential for *Plasmodium* motility and malaria transmission

Y. Kobayashi[1], C.S. Busse[1], A. Binder[2], F. Mikus[2], A. Moll[1], F. Frischknecht[2], R. G. Douglas[1]

[1]Institute of Veterinary Physiology and Biochemistry, Justus-Liebig University Giessen, Germany; [2] Integrative Parasitology, Center for Integrative Infectious Disease Research, Heidelberg University Medical School, Heidelberg, Germany

E-mail: ross.g.douglas@uni-giessen.de

Malaria is one of the most life-threatening tropical diseases and spreads through the transmission of *Plasmodium* between human hosts and the mosquito vector. Blocking *Plasmodium* transmission is a key aspect in effective disease control, yet very few current drugs directly target transmission. Actin-like proteins (Alps) are apicomplexan-specific proteins characterised by several unique regions. However, the importance, functions and stage-specific contributions of Alps in *Plasmodium* progression remain unknown. Here, we characterized the role of Alp1 and Alp2b using the *P. berghei* infection model.

The corresponding genes of *Alp1* and *Alp2b* were knocked-out and the subsequent phenotypic impacts on these parasites were investigated. Remarkably, the absence of Alp1 or Alp2b led to a drastic reduction or complete block of mosquito midgut colonisation respectively. Alp1 was essential for ookinete motility, while Alp2b was crucial for parasite fertilisation but not gametocyte commitment. Alp1 and Alp2b function could be restored by complementation of the corresponding *P. falciparum* orthologue, indicating cross-species conservation. Selected unique regions in *P. berghei* Alp1 were mutated and largely had modest effects on ookinetes, while mutations of selected unique regions of Alp2b prevented exflagellation, implicating these regions as critical contributors to Alp2b function.

Our study reveals the essentiality of these Alps in two different steps of *Plasmodium* transmission.

Aminosteroids from Buxaceae and Apocynaceae as leads to new antiprotozoal drugs: Structural diversity and structure-activity relationships

Justus W. Mukavi, Lizanne Schäfer, Lara U. Szabó, Charles O. Nnadi, Julia B. Althaus and Thomas J. Schmidt*

University of Münster, Institute of Pharmaceutical Biology and Phytochemistry, Corrensstraße 48, 48149 Münster, Germany

*Corresponding & presenting author: thomschm@uni-muenster.de

Aminosteroids and related alkaloids from plants of the families Buxaceae and Apocynaceae were discovered by our group to possess, in many cases, strong activity against *Trypanosoma brucei* (responsible for human African trypanosomiasis and Nagana in cattle), as well as against *Plasmodium falciparum*, the parasite responsible for tropical malaria. From various species of the mentioned families, almost 100 such natural compounds have so far been isolated in our group and tested *in vitro* against the mentioned protozoan parasites [1-6]. This presentation will give an overview on the structural diversity and antiprotozoal activity of these compounds. Based on their chemical structures and the biological activity data from *in vitro* phenotypic assays, quantitative structure-activity relationships (QSAR) were investigated using descriptor- and pharmacophore-based modeling using the MOE software [7] as well as 3D quantitative SAR modelling (3D QSAR) using the open3Dqsar software [8]. The major structural determinants in this set of compounds for high activity against the two parasites will be highlighted and discussed. Besides explaining the activity within this existing set of alkaloids by correlating potency with structural features, predictions of antitrypanosomal and antiplasmodial activity for new compounds, including simplified analogs, are attempted using QSAR models.

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Design, synthesis and evaluation of antiparasitic activity of new heterocyclic phosphomimetic derivatives

Evanthia Chazapi,[1] Nuno Santarem,[2] Theano Fotopoulou,[1] Sara Luelmo,[2] Ricardo Monteiro[2], Vivi Bafiti,[1] George E. Magoulas,[1] Maria Zervou,[1] Theodora Katsila,[1] Kyriakos C. Prousis[1], Joana Tavares[2], Anabela Cordeiro da Silva,[2] Theodora Calogeropoulou[1]

[1]Institute of Chemical Biology, National Hellenic Research Foundation, Greece; [2]Institute for Research and Innovation in Health (i3S), University of Porto, Portugal.
E-mail: tcalog@eie.gr

Leishmaniasis is a neglected tropical disease, endemic in 98 countries worldwide with ~12 million people affected [1]. Miltefosine, an alkylphosphocholine is the only approved oral treatment, however it suffers from several drawbacks [1]. In the present study, applying the bioisosterism principle we replaced the phosphate moiety in alkylphosphocholines by the 4-thiazolidinone privileged pharmacophore [2].

Thus, 32 novel 2,3-substituted 4-thiazolidinone and 3,5-substituted 4-thiazolidinone analogues were synthesized incorporating aliphatic chains or cycloalkyl groups connected through oligomethylene spacers. A tetra-alkyl ammonio group was attached at *N*3, mimicking the choline head group of miltefosine.

The series was screened against *Leishmania infantum* (promastigotes and intracellular amastigotes) and for cytotoxicity using THP-1 human cell line differentiated in macrophages. The evaluation of early *in vitro* ADME-Tox properties of the most potent derivatives involved metabolic stability in pooled human liver microsomes and CYP-mediated activity and toxicity against seven major human liver CYP450 isoforms, while ecotoxicity prediction was performed using Admetlab 3.0 s/w. For the most promising molecules, a snapshot pharmacokinetic analysis was conducted in mice, followed by *in vivo* efficacy studies in mice infected with *L. infantum* amastigote forms.

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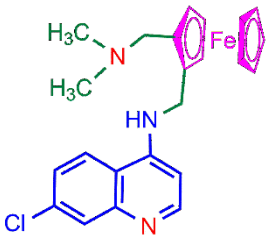
Ferrocene *Cinchona* alkaloid copolymers as anti-parasitic and fluorescence imaging tools

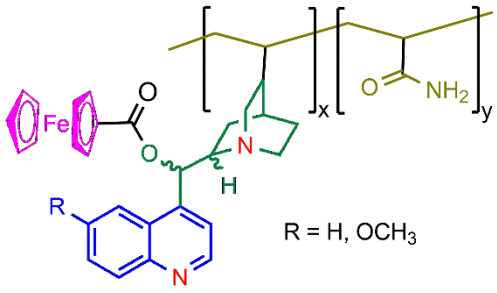
Nicola' Agius and David C. Magri*

Department of Chemistry, Faculty of Science, University of Malta, Malta
E-mail: david.magri@um.edu.mt

Bioorganometallic chemistry holds great promise for the creation of innovative drugs [1]. A notable example is Ferroquine, a compound with a ferrocene moiety incorporated into the lateral side chain of the chloroquine skeleton [2]. Ferroquine is active against chloroquine-sensitive and chloroquine-resistant *P. falciparum* strains and is presently in clinical development for the treatment of malaria. Our interest is the design of intelligent fluorescent natural product copolymers with potential anti-parasitic applications [3]. We postulated this unexploited approach could open new directions in medical research. We previously demonstrated that the antimalarial *cinchona* alkaloids, quinine, quinidine, cinchonine and cinchonidine, are Boolean logic gates with chemicals as inputs and fluorescence as the output [4]. We subsequently polymerized the *cinchona* alkaloids with acrylamide to synthesize logic-based copolymers [5,6]. Remarkably, the bright emissive properties of the *cinchona* alkaloids are conserved within the copolymer in aqueous solution. In our latest findings, the subject of this presentation, we report the physiochemical and logic-based properties of four ferrocene-*cinchona* copolymers [7].



Ferroquine



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Building precision antiparasitics through rational drug design: The ParaX® platform

Natacha Gaillard and Ashwani Sharma

ASTRA Therapeutics AG, Switzerland

E-mails: natacha@astratherapeutics.com, ashwani@astratherapeutics.com

Parasitic diseases in both human and animal health continue to impose a substantial global burden, exacerbated by rising drug resistance and a longstanding stagnation in mechanistically novel antiparasitic therapeutics. Although microtubules play a central role in parasite biology, tubulin has historically remained underexploited as a modern, structure-guided drug target. Recent breakthroughs in structural biology, both experimental and computational, together with the ability to rationally explore a vast chemical multiverse through modern AI, are now transforming conventional drug discovery. Yet these advances remain largely untapped in antiparasitic research, particularly within the Animal Health parasiticide space. This is beginning to change.

In this keynote, we will present a structure-based strategy for designing parasite-selective tubulin inhibitors, enabled by newly solved parasite tubulin-drug complex structures. These structures reveal distinct microenvironmental and conformational features unique to parasite tubulin, establishing clear molecular determinants for safe and selective targeting. Building on this foundation, we integrate experimental structural biology, AI-driven molecular design, and phenotypic/target-based validation into a unified discovery engine-ParaX®-designed to generate novel small molecules with high potency, species selectivity, and favourable safety profiles.

Case studies will illustrate how structure-guided optimization and predictive selectivity modelling accelerate lead identification and deliver resistance-breaking chemical matter. Through this work, ASTRA Therapeutics is positioning itself as a pioneer in applying advanced structural biology and AI-driven chemistry to the largely unexplored frontier of antiparasitic drug design.

Synthesis and antileishmanial activity of 8-aminophenyl-pyrimidopyrimidine-based compounds

André Lopes[1,2], Beatriz Pereira[1], Nuno Santarém[2], Anabela Cordeiro-da-Silva[2], Maria Alice Carvalho[1]

[1]Centre of Chemistry of University of Minho, Campus de Gualtar, Universidade do Minho, 4710-057 Braga, Portugal; [2]Instituto de Investigação e Inovação em Saúde, Universidade do Porto and Institute for Molecular and Cell Biology, University of Porto, 4150-180, Porto, Portugal. Departamento de Ciências Biológicas, Faculdade de Farmácia da Universidade do Porto, Porto, Portugal.
E-mail: id11307@uminho.pt

Leishmaniasis is a neglected tropical disease caused by vector-borne protozoan parasites and continues to represent a growing public health challenge in many developing regions [1]. Current therapeutic options are often limited by suboptimal efficacy, significant adverse effects, and the emergence of drug resistance, underscoring the urgent need for novel treatments [2]. In this context, recent studies have highlighted pyrimidopyrimidine-based compounds as promising anti-*Leishmania* agents [3]. Structure-activity relationship (SAR) analyses have demonstrated that substitutions at the C8 and C4 positions of the core scaffold play a critical role in modulating biological activity. To further expand the SAR and given that the molecular target remains unknown, we pursued a strategy of structural modification of the substituent at the C8 position while maintaining previously explored substituents at the C4 position of the heterocyclic core.

The activity of the new compounds was assessed *in vitro* against *L. infantum* promastigotes and intracellular amastigotes, while cytotoxicity was assessed in THP-1 cells. Highly potent and selective compounds were identified with IC_{50} (promastigotes) = 0.50 mM, IC_{50} (amastigotes) = 4.51 mM, and a selective index higher than 200 and 22, respectively. The synthesis, biological results, and SAR analysis will be presented and discussed. The new insights allowed us to identify promising substitution patterns that can be further optimised to improve the efficacy and safety of this new class of antileishmanials.

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Drug action, drug resistance and drug targeting in animal trypanosomiasis

Marzuq Ungogo[1,2] and Harry P. de Koning[1]

[1]School of infection and Immunity, College of Medical, Veterinary and Life Sciences, University of Glasgow, 120 University Place, Glasgow G12 8TA, United Kingdom.
[2]Current address: University of Edinburgh, Edinburgh, UK
E-mail: Harry.de-Koning@glasgow.ac.uk.

Animal trypanosomiasis is a complex of diseases, endemic from South America through Africa to Asia and the Philippines. It is known as surra, dourine, nagana and mal de calderas among other names [1]. It is caused by *Trypanosoma* species from three different subgenera, including *T. brucei*, *T. evansi*, *T. vivax*, *T. congolense*, *T. equiperdum*, with different (or no) vectors, hosts, tropisms etc. Yet, the resulting differences in pharmacology have been poorly investigated although they greatly impact therapeutic outcomes. Considering the few drugs available, the most efficient use of them must be made – for cure, prophylaxis and to avoid resistance. Here, we present a broad investigation of the differential effects of veterinary trypanocides on the various trypanosome species, document the biochemical causes thereof [2], as well as the exact drug resistance mechanisms for diamidines (e.g. diminazene (Berenil) and pentamidine) and arsenical (melarsoprol, melarsomine) drugs [3,4]. We also present data on cross-resistance between unrelated drugs and give an example how the deliberate targeting of antimetabolites through a transporter that all the relevant *Trypanosoma* species have in common can identify a single lead compound active against all of them [5].

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Novel fosmidomycin analogues with improved bioavailability to target *Toxoplasma gondii*

E. Delgado Betancourt[1], O. Von Rohr[1], T. Quennesson[2], S. Van Calenbergh[2], D. Soldati-Favre[1] and J. Kloehn[1*]

[1]Department of Microbiology and Molecular Medicine, University of Geneva, CMU, Geneva, Switzerland

[2]Laboratory for Medicinal Chemistry (FFW), Ghent University, Ghent, Belgium.

E-mails: Dominique.Soldati-Favre@unige.ch; Joachim.Kloehn@unige.ch

Fosmidomycin is an antibiotic and potent antimalarial that inhibits 1-deoxy-D-xylulose 5-phosphate reductoisomerase (DXR) in the methylerythritol phosphate (MEP) pathway of isoprenoid synthesis. This pathway is essential in most bacteria and in apicomplexan parasites that retain an apicoplast, including *Toxoplasma gondii*. Although *T. gondii* relies on the MEP pathway, fosmidomycin is ineffective against this parasite due to poor parasite membrane permeability [1].

To overcome this limitation, fosmidomycin analogues were synthesized [2] with potentially improved membrane permeability. Of the 24 novel compounds tested, three displayed anti-*Toxoplasma* activity at 10 µM, arresting parasite replication and reducing or eliminating lysis plaque formation. Their activity was rescued by mevalonate supplementation in parasites engineered to express a mevalonate bypass pathway [3,4], confirming DXR as the molecular target.

To assess activity against the slow-growing bradyzoite stage cultured in myotubes, we used heavy-water labeling coupled with gas chromatography-mass spectrometry (GC-MS) to quantify deuterium incorporation into DNA-derived deoxyribose as a sensitive measure of parasite replication in mature cysts [5]. Preliminary data indicate that these analogues exhibit modest anti-bradyzoite activity and are less effective than other drugs of similar molecular weight, such as doxycycline. Our ongoing work aims to define essential and druggable apicoplast functions during chronic *Toxoplasma* infection. Together these findings underscore stage-specific differences in drug susceptibility and highlight the importance of testing candidate drugs in physiologically relevant models.

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Keynote Talk

Advancing anthelmintic discovery through parallel tracks of target identification and phenotypic screening

Kaetlyn T Ryan[1], Elena G Rehborg[1], Bailey Clair R Henthorn[1], Nathalie Dinguirard[1], Bailey Bell[2], Douglas Braun[2], Kathy Vaccaro[1], Tim S Bugni[2], Mostafa Zamanian[1]

[1] Department of Pathobiological Sciences, University of Wisconsin-Madison

[2] College of Pharmacy, University of Wisconsin-Madison

The stagnation of the anthelmintic pipeline and the rise of drug resistance necessitate a multi-pronged approach to discovery that explores both novel chemical space and untapped biological targets. We outline two parallel projects addressing this need: a target-based approach focused on the molecular determinants of parasite behavior and a whole-organism approach focused on marine microbial chemistry. In the first track, we leverage tissue-targeted transcriptomics and behavioral assays to resolve receptor-level control of sensory and secretory biology in filarial nematodes. This work has identified chemosensory and aminergic GPCRs as central regulators of parasite-host communication, while establishing heterologous platforms for deorphanizing and screening these potential targets. Parallel to these efforts, we are conducting multi-dimensional phenotypic screens of microbial natural products from unique marine ecological niches. Screening of understudied marine bacterial genera has identified lead candidates with potent, multi-stage activity that induce unique morphological phenotypes. Collectively, these distinct discovery tracks can help expand the landscape of available anthelmintic targets and leads.

A high-throughput anthelmintic screening pipeline uncovers novel and repurposed anthelmintics targeting filarial and intestinal parasites

Hala Fahs[1,2], Fathima Refai[1], Suma Gopinadhan[1], Yasmine Moussa[1], Yamanappa Hunashal[1], Gennaro Battaglia[1], Patricia G. Cipriani[1,2], Gennaro Esposito[1], Mostafa Zamanian[3], Jennifer Keiser[4], Antony Page[5], Kristin C. Gunsalus[1,2], Fabio Piano[1,2]

[1]New York University Abu Dhabi, UAE, [2]New York University, USA, [3]University of Wisconsin-Madison, UK, [4]Swiss Tropical Institute, Switzerland, [5]University of Glasgow, UK
E-mail: Hala.fahs@nyu.edu

Helminths infect an estimated 1.5 billion people and severely impact livestock and companion animals. The growing emergence of anthelmintic resistance is alarming, highlighting the urgent need for treatments with novel mechanisms of action. Using the NYUAD high-throughput screening platform, we screened 50,000 compounds with a focus on broad-spectrum activity. This led to the identification of multiple nematicidal molecules and chemical classes with novel mechanisms of action, highlighting the promise of targeting new pathways for anthelmintics. First, a set of avocado fatty alcohols/acetates (AFAs) is effective against veterinary parasites *in vitro* and *in vivo* [1]. Genetic and biochemical tests revealed that AFAs inhibit POD-2, an acetyl CoA carboxylase (ACC), the rate-limiting enzyme in lipid biosynthesis. Second, another candidate, ChemAD-16, exhibited potent embryonic and larval lethality in *Caenorhabditis elegans* and *Haemonchus contortus*, and it showed microfilaricidal activity against the heartworm *Dirofilaria immitis*. Third, a family of antifungal compounds was effective across multiple parasites, offering promising potential for repurposing. All candidate compounds were effective against both anthelmintic-resistant *C. elegans* strains and field-derived multi-drug-resistant *H. contortus* (UGA), indicating that they act through novel targets. These novel compounds offer promising directions for the development of anthelmintic drugs, either as standalone therapies or in combination. Moreover, targeting multiple pathways with drug cocktails may enhance treatment efficacy while potentially helping mitigate the rise of anthelmintic resistance.

[1] Fahs et al. 2025. Nat Commun. 16(1):305. doi: 10.1038/s41467-024-54965-w.

Strategic collaboration to develop ecologically sustainable antiparasitic solutions from microbial natural products

M. Spohn[1], S. Noack[2], R. J. Marhöfer[2], P. M. Selzer[2], T. F. Schäberle[1], Y. Moreno[3], D. Bruhn[3], M.A. Patras[1], J. Tognetti[4], H. F. Koolman[4], S. Mihajlovic[1], M. Marner[1].

[1]Fraunhofer Institute for Molecular Biology and Applied Ecology, Branch for Bioressources, Gießen, Germany; [2] Boehringer Ingelheim Vetmedica GmbH, Ingelheim am Rhein, Germany; [3] Boehringer Ingelheim Animal Health USA Inc., Athens GA, USA; [4] Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

Email: marius.spohn@ime.fraunhofer.de

Animal parasites are not only a nuisance but also pose significant health risks, as they can seriously affect the well-being of pets and livestock, cause substantial economic losses, and in some cases transmit infectious diseases from animals to humans. To develop ecologically sustainable antiparasitic solutions, Boehringer Ingelheim Animal Health has entered a strategic research collaboration with Fraunhofer IME. This partnership integrated Fraunhofer's extensive microbial resources - one of the world's most important microbial collections - and advanced analytical technologies for natural product discovery into Boehringer's innovation program, aiming to identify and develop novel natural-product–based antiparasitics.

Jointly, we execute a metabologenomic-assisted natural product discovery campaign by profiling fungal and bacterial crude extracts for activity against endo- and ecto-parasites. The bioprospecting process is rigorously surveilled by the team to guarantee Access and Benefit-Sharing compliance. Selected active extracts are subjected to UPLC microfractionation coupled with UV and HR-MS/MS detection, and individual fractions are re-screened, enabling the efficient identification of bioactive natural products with minimal material requirement. Compounds showing activity that cannot be confidently dereplicated from the UV and HR-MS/MS data are subsequently taken forward for isolation and structural elucidation by NMR. To date, our program has revealed a wide range of natural product structures, including known antiparasitics as well as compounds that have not yet been explored for their antiparasitic potential.

Strevertene A, a Streptomyces-derived macrolide with selective activity against the human parasite *Schistosoma mansoni*

Felix Mühlemeyer[1], Yang Liu[1], Celine M. Zumkeller[1,2], Bernardo P. Moreira[3], Francesca Magari[4], Kornelia Hardes[2], Marius Spohn[1,2], Simone Häberlein[3], Till F. Schäberle[1,2] and Michael Marner[1,2]

[1]Institute for Insect Biotechnology, Justus-Liebig-University Giessen; [2]Branch for Bioresources of the Fraunhofer Institute for Molecular Biology and Applied Ecology; [3]Institute for Parasitology, Justus-Liebig-University Giessen; [4]Institute of Pharmaceutical Chemistry, Philipps University Marburg
E-mail: felix.muehlemeyer@ernaehrung.uni-giessen.de

Schistosomiasis, a neglected tropical disease caused by parasitic blood flukes, affects 250 million humans worldwide, leading to widespread chronic illness and disability [1]. Praziquantel is the only drug to cure patients suffering from schistosomiasis, but reports of reduced efficacy underscore concerns about the future therapy [2]. To identify alternative compounds with antischistosomal activity, almost 1000 bacterial and fungal extracts were screened against adult *Schistosoma mansoni* worm pairs.

This effort revealed *Streptomyces sp.* ST501019 as a producer of strevertene A, a 28-membered pentaene macrolide. Strevertene A displayed detachment of adult worms, pair separation and a minimum motility inhibition concentration of 14 µM. Most intriguingly, we observed potent *in vitro* activity against schistosomula (IC_{50} = 4 µM), a larval developmental stage of Schistosoma which is significantly less susceptible to praziquantel. Strevertene A exhibits a selectivity index (schistosomula activity over human cell toxicity) of more than 10 (HepG2 CC_{50} = 42 µM). Moreover, it showed no toxicity against *Caenorhabditis elegans* up to 110 µM. Genome sequencing of ST501019 identified the corresponding polyketide synthesis gene cluster and allowed to derive a biosynthesis hypothesis.

This study demonstrated for the first time the selective antischistosomula activity of strevertene A, identified through a microbial natural product based screening against *Schistosoma mansoni*.

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Keynote Talk

The metabolism of *Echinococcus* and novel targets for treatment of echinococcosis

Britta Lundström-Stadelmann

Institute of Parasitology, Department of Infectious Diseases and Pathobiology, Vetsuisse Faculty, University of Bern, Bern, Switzerland;
Multidisciplinary Center for Infectious Diseases, University of Bern, Bern, Switzerland
Email: Britta.lundstroem@unibe.ch

The zoonotic cestodes *Echinococcus multilocularis* and *E. granulosus* s. l. cause alveolar and cystic echinococcosis, respectively, severe diseases of major public health and veterinary concern. Despite relatively low global human case numbers, both rank among the top food-borne parasites worldwide. Current therapies are mainly parasitostatic and poorly target parasite stem cells, necessitating lifelong treatment with frequent side effects. Novel, parasite-specific drugs are urgently needed.

We established a robust whole-organism drug screening platform for *Echinococcus* spp., integrating efficacy assays that measure metacestode damage-marker release, metacestode and stem cell viability, and *in vivo* efficacy in mouse models. Screening >1,700 repurposed compounds identified promising candidates like mefloquine, buparvaquone, ESI-09, and niclosamide. While only mefloquine showed efficacy in mouse models, mechanistic studies revealed that buparvaquone inhibits the mitochondrial electron transport chain, and ESI-09 and niclosamide functions as mitochondrial uncouplers, highlighting parasite energy metabolism as a key vulnerability.

Further research identified mitochondrial malate dismutation (MD), an oxygen-independent pathway absent in mammals, as a promising target. Our current focus explores the biosynthesis of rhodoquinone, a key electron carrier in the MD pathway, as a novel drug target. Threonine is highly utilized by the parasite and promotes its growth, making threonine metabolism another potential target we investigate.

Thus, our studies reveal crucial metabolic dependencies of *Echinococcus* spp. and point toward new therapeutic strategies that could overcome current limitations in echinococcosis treatment.

Succinate dehydrogenase activity in helminths is inhibited *in vitro* by triclabendazole and its metabolites

Tobias Kämpfer[1,2], María Eugenia Ancarola[1], Pascal Zumstein[1,2], Alice Bernal[1,2], Trix Zumkehr[1], Seraina Mühlemann[1], Natalie Wiedemar[1,3], Britta Lundström-Stadelmann[1,3]

[1]Institute of Parasitology, Department of Infectious Diseases and Pathobiology, Vetsuisse Faculty, University of Bern, Switzerland; [2]Graduate School for Cellular and Biomedical Sciences (GCB), University of Bern, Switzerland; [3]Multidisciplinary Center for Infectious Diseases, University of Bern, Switzerland.
E-mail: britta.lundstroem@unibe.ch; maría.ancarola@unibe.ch

In parasitic organisms, mitochondrial energy metabolism may vary throughout their life cycle. Mitochondrial complex II acts as a succinate dehydrogenase (SDH) while under low-oxygen conditions it can act as a fumarate reductase. This reverse reaction is critical for parasitic worms yet negligible in their hosts, offering an attractive druggable target.

Searching for novel treatments against the cestode *Echinococcus multilocularis*, we screened 20 benzimidazoles for *in vitro* inhibition on SDH activity of the disease-causing stage of *E. multilocularis*, other helminths and mammalian organisms.

We observed that SDH activity was inhibited in mitochondria from *E. multilocularis* metacestode vesicles by triclabendazole (TCBZ) and its metabolites (TCBZ-sulfoxide and TCBZ-sulfone), whereas it remained above 80% for all other benzimidazoles.

We next tested TCBZ, albendazole, and their metabolites on mitochondria from other organisms. TCBZ and its metabolites inhibited SDH activity across all tested helminths (trematodes and nematodes), and mammalian species.

Sequence analysis revealed that all SDH subunits are largely conserved among species. Slight differences at the quinone-binding site reflect the use of an alternative quinone (such as rhodoquinone) by helminths.

In summary, TCBZ is a promising compound for the development of new therapies against helminth infections, however, toxic effects on mammalian mitochondrial function may also occur.

Identification and characterization of cMDH as a putative drug target in alveolar echinococcosis

Pascal Zumstein[1,2], Laura Vetter[1], Maria Eugenia Ancarola[1],
Britta Lundström-Stadelmann[1,3]

[1]Institute of Parasitology, University of Bern, Switzerland
[2]Graduate School for Biomedical and Cellular Sciences, University of Bern, Switzerland
[3]Multidisciplinary Center for Infectious Diseases, University of Bern, Switzerland
E-mail: britta.lundstroem@unibe.ch

Alveolar echinococcosis (AE), caused by the larval stage (metacestode) of the cestode parasite *Echinococcus multilocularis*, is a life-threatening disease with limited drug treatment options. Like other helminths, *E. multilocularis* relies heavily on anaerobic metabolism including the malate dismutation pathway. Here, we investigated cytosolic malate dehydrogenase (cMDH) as a key component of this pathway.

Expression analyses based on qPCR of putative *E. multilocularis* cMDH homologs revealed high expression levels of EmuJ_000417100. This homolog was recombinantly expressed, purified and its catalytic activity was confirmed. *In vitro*, oxaloacetate reduction to malate was favored, as low Michaelis-Menten constants (K_m (OAA) = 16.4 ± 3.2 µM and K_m (NADH) = 11.5 ± 3.9 µM) and high enzymatic efficiency (K_{cat}/K_m = 6.6 x 10^6 $M^{-1}s^{-1}$) was observed.

Functional relevance was supported by RNA interference experiments, where knock-down of cMDH expression in primary cell cultures significantly impaired parasite development and growth. Furthermore, treatment with gossypol, a potent oxireductase inhibitor, significantly reduced recombinant cMDH activity in a dose-dependent manner (IC_{50} = 0.28 ± 0.09 µM) and induced parasite death in primary cell cultures (IC_{50} = 5.93 ± 0.30 µM).

In conclusion, our results identify cMDH as a promising metabolic drug target and provide a foundation for the development of selective inhibitors against *E. multilocularis* cMDH.

From omics to targets to drugs: strategies to fight liver flukes

Svenja Gramberg, Oliver Puckelwaldt, Sagar Ajmera, Simone Haeberlein

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

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) [1]. 2024). Differential gene expression analysis identified 15 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 and muscle 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 the calcium channel $TRPM_{PZQ}$) 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 muscle-associated PKs 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 [2]. Taken together, our new omics datasets can serve as playground for the discovery of druggable genes that serve as Achilles' heels in this parasite.

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Dual proteomic and chemical-genetic evidence identifies proteases as druggable drivers of *Trypanosoma cruzi* egress

Sara De Grandis[1], Delia Bogenstätter[1], Gaëlle Lentini[1]

1 Institute of Cell Biology, University of Bern, Bern, Switzerland
Email: gaelle.lentini@unibe.ch

Trypanosoma cruzi, the causative agent of Chagas disease, is a highly successful parasite, circulating through extensive sylvatic and domestic transmission cycles. The final stage of its intracellular cycle is marked by differentiation into trypomastigotes and the release of hundreds of infectious forms. While host cell lysis was long thought to result solely from mechanical rupture, emerging evidence suggests that egress is an actively regulated, parasite-driven process orchestrated by the secretion of parasite effectors [1, 2].

We developed an automated quantitative pipeline and a set of phenotypic assays that allow detailed dissection of the egress process [3]. Screening a protease inhibitor library, we identified five compounds that inhibit egress by >90%. Our findings point toward a parasite intramembrane-cleaving protease (I-CLiP) as a key regulator of egress. We hypothesize that intracellular parasites accumulate effector molecules in the flagellar pocket, the sole site of exocytosis, and release them at the onset of egress in a I-CLiP activity-dependent manner. Comparative proteomic studies revealed distinct signatures between mature intracellular parasites and freshly egressed one, identifying candidate secreted effectors, including two transmembrane proteases. Ongoing work using transgenic parasites and characterization of the inhibitors aims to validate their roles in regulating egress. Together, our findings highlight proteases as central regulators of *T. cruzi* egress and underscore their promise as novel therapeutic targets for Chagas disease.

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Multi-target drug discovery against *Babesia divergens*: targeting invasion, egress, and proteostasis

Pavla Šnebergerová[a,b], Luise Robbertse[a] ,Tereza Kozelková[a,b] , Pavla Fajtová[e,] Ana Maria Filipe[a,b], Alper Dede[a,b], Viktoriya Levytska[a], Masahito Asada[c], Kayode K.Ojo[d], Jehad Almaliti [f], Momen Al-Hindy [f], William H Gerwick [f], Marie Jalovecká[a,b], Anthony J O'Donoghue[e] and Daniel Sojka[a]*

[a] Institute of Parasitology, Biology Centre of the Czech Academy of Sciences, České Budějovice, Czech Republic; [b]Faculty of Science, University of South Bohemia in České Budějovice, České Budějovice, Czech Republic; [c]National Research Center for Protozoan Diseases, Obihiro, Japan; [c]University of Agriculture and Veterinary Medicine, Obihiro, Japan; [d] Department of Medicine, Division of Allergy and Infectious Disease, Center for Emerging and Reemerging Infectious Disease (CERID), University of Washington, Seattle, US; [e]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, California, US; [f]Center for Marine Biotechnology and Biomedicine, Scripps Institution of Oceanography, University of California, San Diego, California, US.

Tick-transmitted Babesia divergens is a major cause of bovine babesiosis and an emerging zoonotic threat in humans. With limited therapeutic options and increasing concern over resistance, selective anti-babesial strategies aligned with a One Health framework are urgently needed. Here, we highlight three druggable parasite pathways controlling invasion, egress, and proteostasis.

First, we investigated clade-C aspartyl proteases BdASP3a/b, homologs of *Plasmodium* plasmepsins IX/X and *Toxoplasma gondii* ASP3. BdASP3a/b are expressed in erythrocytic stages and localize to the apical complex. Recombinant BdASP3 proteins show proteolytic activity, and only BdASP3b is inhibited by the PfPMX-targeting compound 49C, causing accumulation of extracellular merozoites and supporting a key role in invasion and secretory protein maturation.

Second, we characterized four *B. divergens* calcium-dependent protein kinases (BdCDPK1–4), all featuring small gatekeeper residues enabling selective inhibition by bumped kinase inhibitors (BKIs). Among six BKIs tested, BKI-1294 showed the strongest activity and selectively inhibited BdCDPK4, blocking parasite egress while permitting continued intracellular replication and formation of multinucleated complexes, consistent with a conserved egress regulatory function.

Finally, we evaluated the Babesia proteasome as an essential drug target by screening several novel generations of peptide epoxyketone inhibitors derived from the marine natural product carmaphycin B. Selected compounds inhibited proteasomal β5 activity in *B. divergens* and *B. microti* lysates in the low-nanomolar range, showed carfilzomib-like potency against the purified *B. divergens* proteasome, suppressed parasite growth in bovine erythrocyte cultures, and exhibited reduced toxicity toward human cells, supporting an improved therapeutic window.

Together, these data establish BdASP3s, BdCDPK4, and the Babesia proteasome as actionable targets for selective chemotherapy against babesiosis.

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Classic metabolic vulnerabilities in dormant and pan drug-tolerant *Toxoplasma gondii* tissue cysts revealed by drug screening, proteomic and metabolomic analysis

Deborah Maus[1], Elyzana Putrianti[1], Janina Jocks[1], Erik Andrae[1], Tobias Hoffmann[2], Michael Laue[2], Frank Seeber[3], Martin Blume[1]

[1] Metabolism of Microbial Pathogens, Robert Koch Institute, Berlin, Germany
[2] Advanced Light and Electron Microscopy, Centre for Biological Threats and Special Pathogens 4, Robert Koch-Institute, Berlin, Germany
[3] Mycotic and Parasitic Agents and Mycobacteria, Robert Koch Institute, Berlin, Germany
E-mail: blumem@rki.de

Toxoplasma gondii is a globally important pathogen infecting humans and virtually all warm-blooded animals. The clinically silent parasite tissue cysts remain life-long in neural and muscle tissues and cannot be eradicated by any current medical treatments. They can give rise to potentially life-threatening acute Toxoplasmosis in immune-weakened individuals and underly transmission to humans via undercooked meat products.

We developed a novel *in vitro* model to raise fully drug tolerant tissue cysts in human skeletal muscle cells and screened more than 700 compounds from the MMV Pathogen Box, myxobacterial compounds and repurposed drugs against tissue cysts. We confirmed several compounds that are active against acute and chronically infectious stages of the parasite at nanomolar concentrations. A combination of metabolomics-, proteomics- and chemical genomics-based target identification efforts revealed mitochondrial translation, the *bc1*-complex and folate metabolism as shared vulnerabilities. We also find several identify compounds with unknown or putative non-metabolic modes of actions.

Together, our data suggests the presence of a metabolic Achilles heels in the previously deemed metabolically inactive excysted parasite stage that can be translated to viable treatment strategies. It also identifies the pharmacokinetic limitations of current therapies, rather than parasite tolerance, as the primary driver of their failure to eradicate Toxoplasma cysts.

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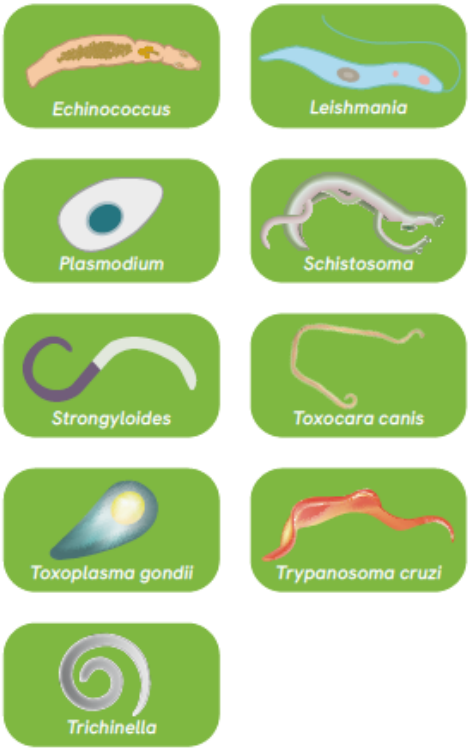
Plasmodium	●		
Schistosoma	●		●
Strongyloides	●		
Toxocara canis	●	●	
Toxoplasma gondii	●		●
Trypanosoma cruzi	●		
Trichinella	●		

*ELISA: *Echinococcus* spp.; immunoblot: *Echinococcus* spp., differentiation between *E. granulosus* and *E. multilocularis*



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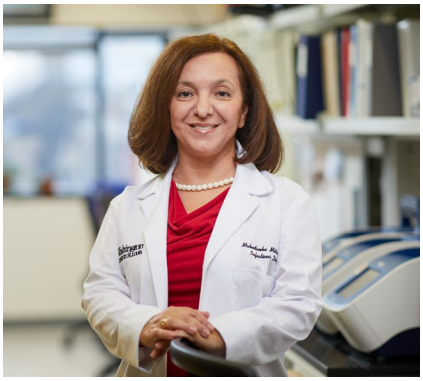
Keynote Talk

GPCR antagonists with potent *in vitro* and *in vivo* macrofilaricidal activity



Makedonka Mitreva[1], Bruce A Rosa[1], Zhenfu Han[1], Ashutosh Arun[1], Fidelis Cho-Ngwa[2], Nancy Tricoche[3], Ricardo Peguero[3], Victoria Banas[1], Melanie Shadrick[1], Sara Lustigman[3] and James W. Janetka[1]

[1]Washington University School of Medicine, St. Louis, MO, USA; [2]University of Buea, Buea, Cameroon and [3]New York Blood Center, New York, NY, US

E-mail: mmitreva@wustl.edu

Chronic filarial infections remain a global health burden, with limited adulticidal therapies highlighting the need for new drugs. Our omics-driven prioritization and phenotypic screening of an FDA-approved library of compounds against *Brugia pahangi* adult worms *in vitro* identified 18 antifilarial hits, including several drugs targeting G-protein Couple Receptors (GPCRs). We expanded on these findings by advancing hit-to-lead studies across these structurally diverse GPCR antagonist classes. Specifically, we explored repurposing human GPCR antagonists clemizole (CLE), pimozide (PMZ), proroxan (PRO), and suloctidil (SUL), and 45 rationally-designed analogs for activity against *Brugia pahangi* and two *Onchocerca* species. Of those, 27 showed *in vitro* adulticidal activity. *In vivo*, CLE and analog C-8 reduced worm burden by 60.5% and 50.8%, respectively, while S-17 (SUL analog) and PMZ-6 (PMZ analog) modestly reduced worm burden (36% and 25%, respectively), but all three significantly reduced worm fecundity. Transcriptional profiling revealed lasting upregulation of stress responses and downregulation of potential target GPCRs in C-8 treated worms. Radioligand binding assays revealed selective human GPCR affinities, with CLE and SUL analogs having increased parasite selectivity. PRO and PRO-1 showed high alpha-adrenergic receptor affinity, while PMZ analogs were less selective. CLE, C-8 and S-17 represent promising leads for further optimization as antifilarial drugs. While target identification remains ongoing, our findings validate this multidimensional approach for antifilarial drug discovery. Ongoing work focuses on confirming molecular targets, optimizing lead compounds, and exploring species-specific activity to advance these candidates toward clinical development.

Dual mechanism of niclosamide in targeting the *Wolbachia*–filarial worm symbiosis

Denis Voronin

Systems Genomic Section, LPD, NIAID, NIH, Bethesda, USA

Lymphatic filariasis continues to be a major global health challenge due to the lack of effective macrofilaricidal drugs that eliminate adult worms. The survival and reproduction of adult filarial worms depend on their intracellular endosymbiont, *Wolbachia*, which makes this bacterium an attractive therapeutic target. In this study, we explored two complementary strategies to disrupt the *Wolbachia*–parasite symbiosis: (1) a host-oriented approach that enhances autophagy, an intracellular defense mechanism that degrades endosymbiotic bacteria, and (2) a direct bacterial targeting approach using niclosamide, a repurposed FDA-approved drug and its analogs.

First, we screened autophagy-inducing compounds *in vitro* on adult female *Brugia pahangi* worms to evaluate their effects on *Wolbachia* density, motility, and reproductive fitness. Niclosamide and its ethanolamine salt (NEN) exhibited the strongest activity at the lowest concentrations (1 μM). Both compounds also significantly induced the expression of lysosome-associated membrane protein (LAMP), confirming the activation of autophagy and supporting the host-directed mechanism that disrupts the *Wolbachia*-parasite symbiosis.

In parallel, computational structural analyses revealed that niclosamide can directly bind to *Wolbachia* membranal proteins, suggesting it may interfere with bacterial secretion systems and viability. This dual mode of action—activating autophagy within the parasite while directly inhibiting the bacteria—provides a mechanistic basis for repurposing niclosamide as a candidate for macrofilaricidal therapy.

Future research will use machine learning-based modeling to predict and optimize niclosamide analogs that have improved bioavailability and enhanced efficacy and specificity towards *Wolbachia*. This approach aims to accelerate the design of next-generation therapeutics for the elimination of filarial diseases.

Chemical probes to study the role of the lysine demethylase LSD1 in *Leishmania* infection

Adina A. Baniahmad[1], Maria Gutiérrez-Sanchez, Eric Prina[2], Eric Metzger[3], Roland Schüle[3], Gerald Spaeth[2], Manfred Jung[1]

[1]University of Freiburg/ Institute of Pharmaceutical Sciences, Freiburg, Germany
[2]Institute Pasteur/ Department of Parasites and Insect Vectors, Paris, France
[3]University of Freiburg Medical Center/ Department of Urology, Germany, Freiburg
E-mail: manfred.jung@pharmazie.uni-freiburg.de

Epigenetic mechanisms are involved cancer but also microbial infections. In order to promote their survival, many viral, bacterial, and eukaryotic pathogens alter the gene expression profile of their host. The mechanisms causing host cell subversion are still poorly understood, despite grave repercussions for human health. Parasites of the genus *Leishmania* subvert the function of the macrophage Lysine Specific Demethylase 1 (LSD1) to establish permissive conditions for parasite survival [1]. LSD1 (aka KDM1A) is a FAD-dependent amine oxidase that removes methyl groups from mono- and dimethylated lysine 4 and 9 residues of histone H3 (H3K9/4me1me2) [2]. It was shown that a leishmania infection causes histone H3 demethylation at the activating H3K4 and repressive H3K9 marks which is linked with the suppression of inflammatory gene expression [3]. By developing inhibitors of LSD1, the pathogenic mechanism of Leishmania could be reversed and these could then be recognized and destroyed by macrophages without destroying the macrophage itself. For assessment of target engagement, fluorophore-labeled LSD1 probes were designed and utilized in NanoBRET assays.

AAB and MJ thank the Deutsche Forschungsgemeinschaft (DFG, Ju295/17-1) for funding.

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Drug repurposing for kala-azar, malaria and toxoplasmosis potential treatments

Biljana Arsic[1,2*], Andreas Maier[2], Michael Hartung[2], Jan Baumbach[2,3]

[1]Department of Chemistry, Faculty of Sciences and Mathematics, University of Niš, Višegradska 33, 18000 Niš, Serbia; [2]Institute for Computational Systems Biomedicine, University of Hamburg, Albert-Einstein-Ring 8-10, 22607 Hamburg, Germany; [3]Computational Biomedicine Lab, Department of Mathematics and Computer Science, University of Southern Denmark, 5230 Odense, Denmark

*E-mail: biljana.arsic@pmf.edu.rs

Neglected tropical diseases (NTDs) are a broad group of illnesses caused by many types of pathogens. They affect over 1 billion people worldwide, and about 1.5 billion individuals currently need preventive or curative NTD treatments [1]. Kala-azar (caused by *Leishmania donovani*), malaria, and toxoplasmosis treatments are currently limited due to the toxicity of the treatments (kala-azar), resistance (malaria), or the inability to completely remove the parasite from the body (toxoplasmosis).

Lists of kala-azar, malaria, and toxoplasmosis-associated genes were downloaded from the DisGeNET database [2]. Human genes relevant to diseases were identified using the DOMINO algorithm [3]. Drug repurposing analyses were conducted *via* the Drugst.One platform by using the “Drug Search” module. Different algorithms were applied twice, once for approved drugs only and once for a combination of approved and unapproved drug sets [4]. Interaction data were retrieved from multiple sources depending on interaction type.

STAT3 was found to be an essential gene in all three infections [5-7]. The most frequently seen candidate drug in analyses is nifuroxazide, currently in use for the treatment of acute diarrhoea and infectious traveller diarrhoea or colitis [8].

Further *in vitro* and *in vivo* studies will show the efficacy of this drug repurposing method.

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The RNA helicase eIF4A as a target for the development of pan-antivirals and anti-pathogenic drugs – From natural compounds to new eIF4A inhibitors

Arnold Grünweller

Institute of Pharmaceutical Chemistry, Philipps University Marburg, Marbacher Weg 6, 35032 Marburg, Germany
Email: arnold.gruenweller@staff.uni-marburg.de

The identification of potent antivirals and antipathogenic compounds is a global challenge of outstanding importance and an urgent need in drug development.

One very interesting target is the RNA helicase eIF4A, a component of the translation initiation complex eIF4F, which unwinds stable RNA structures in the 5´-UTRs of selected mRNAs to enable protein synthesis. Many highly pathogenic RNA viruses and several other important pathogens depend on the unwinding activity of eIF4A for efficient protein synthesis making this helicase a very promising drug target.

Potent eIF4A inhibitors, such as the rocaglates and pateamines, have already been shown to inhibit RNA virus replication. These compounds also inhibit the reproduction of several pathogens, like *Candida, Toxoplasma* or *Trypanosoma*, efficiently at low nanomolar concentrations through a mechanism known as RNA-clamping [1-5]. Currently, we have used these inhibitors to treat schistosomes or flies like *Aedes aegypti* that serve as vectors for the transmission of arboviruses.

A key challenge with existing eIF4A inhibitor classes is their complex structure and costly synthesis as well as their limited bioavailability. To address these drawbacks, we conducted an extensive drug discovery campaign aimed at identifying new eIF4A inhibitors. We applied multiple strategies, including fragment-, ligand-, and structure-based approaches. After virtual screening of compound libraries spanning an ultra-large chemical space of 2.3 trillion molecular structures, top-scoring molecules were tested through our in-vitro and cell-based assay pipeline, which includes Thermal Shift Assay, Cytotoxicity Assay (WST-1) and Dual-Luciferase Reporter Assay. Promising candidates were further tested for antiviral activity.

To date, we have identified 16 hits as putative new eIF4A inhibitors showing antiviral activities in the low micromolar to high nanomolar range. We are now optimizing these initial hits to develop lead candidates with nanomolar potency, improved bioavailability, and more efficient synthesis routes compared to known eIF4A inhibitors.

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Evaluation of the RNA helicase eIF4A as potential drug target in *Schistosoma mansoni* and its inhibition by rocaglates and pateamines

S. Welsch[1], F. Magari[2], S. Haeberlein[1], A. Grünweller[2], C. G. Grevelding[1]

[1] Institute of Parasitology, Justus Liebig University Giessen, Germany
[2] Institute of Pharmaceutical Chemistry, Philipps University Marburg, Germany
E-mail: sophie.welsch@vetmed.uni-giessen.de

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. Inhibition of the eukaryotic translation initiation factor 4A (eIF4A) by rocaglates has been shown to exhibit antipathogenic potential [1]. Furthermore, previous work using RNA interference showed that eIF4A of *S. mansoni* (SmeIF4A) is an essential factor for stem-cell activity and reproduction [2]. For further analysis, inhibition of SmeIF4A by plant-derived rocaglates or the marine compounds called pateamines was investigated using thermal shift assays (TSA). The anti-schistosomal potential of these compounds was analyzed by treating adult *S. mansoni in vitro* while examining vitality parameters, stem-cell proliferation, and miracidia-hatching rates.

TSA revealed an increase (> 5°C) in the thermal stability of recombinant SmeIF4A upon incubation with rocaglates or pateamines, confirming that SmeIF4A is a target of these compounds. Treatment of adult worms resulted in reduced attachment ability and motility. Also, stem-cell proliferation was impaired, as demonstrated by reduced numbers of EdU^+ cells. Rocaglate and pateamine treatment finally reduced the number of hatched miracidia *in vitro*, indicating that embryogenesis was compromised.

Our results demonstrate the potential of rocaglates and pateamines against adult *S. mansoni in vitro* and SmeIF4A as an interesting target. This may open new perspectives for drug development.

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Repurposing of fosfomycin for filarial infections

Frederic Risch[1,2], Hannah R. Wegner[1], Benjamin Lenz[1], Tilman Aden[1], Achim Hoerauf [1,2], Marc P. Hübner[1,2]

[1] Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Bonn, Germany

[2] German Center for Infection Research (DZIF), partner site Bonn-Cologne, Bonn, Germany

E-mail: Frederic.risch@ukbonn.de

Background & Aim

Filarial infections such as lymphatic filariasis and onchocerciasis are responsible for millions of disability adjusted life years. Doxycycline requires 4-6 weeks of consecutive administration to be curative. Therefore, new compounds are urgently needed to facilitate the elimination of human filarial infections. Since financial resources are limited during drug development, it can be beneficial to repurpose registered drugs.

We investigated the efficacy of fosfomycin, an antibiotic commonly used for urinary tract infections, in a filarial rodent model.

Methods

BALB/c mice were naturally infected with *Litomosoides sigmodontis* and treated orally with fosfomycin 2-3 times per day for 14 days starting either 1 day (efficacy vs infective stage) or 35 days post infection (efficacy vs adult worms). The worm burden and changes in *Wolbachia* numbers were analyzed *ex vivo* 4-5 weeks after treatment start.

Results

Early treatment with fosfomycin led to a reduction of the median worm burden by 96% (twice daily) or 100% (thrice daily treatment) compared to the vehicle control. A comparative treatment with doxycycline had no impact on the number of recovered worms.

The fosfomycin treatment that was targeted against adult worms showed no impact on the number of recovered worms, and qPCR analysis of both treatment timepoints demonstrated no reduction of *Wolbachia*. Further optimizations of the treatment regimen against adult worms are needed.

Combination-based Cry-based anthelmintic therapies

Kelly A Flanagan; Ernesto R Soto; Florentina Rus; Qian Ding; Nicholas Cazeault; Hanchen Li; Gary Ostroff; Raffi V Aroian

Program in Molecular Medicine, University of Massachusetts Medical School, MA, USA
E-mail: Raffi.aroian@umassmed.edu

Gastrointestinal nematodes (GINs) are parasitic nematodes that cause significant morbidity among livestock and impoverished humans worldwide. Nematode resistance to the few existing drugs is increasing globally, and new drugs are urgently needed. To date six anthelmintic (Cry) proteins have been discovered in *Bacillus thuringiensis* (Bt) that are bioactive against GINs and clear GIN infections *in vivo*. Here we present ongoing studies to reveal synergistic bioactivity against GINs between nematicidal Cry proteins. In nature, Cry proteins almost always occur in combinations, suggesting such combinations are functionally relevant. We are screening *Ancylostoma ceylanicum* hookworms and *Trichuris muris* whipworms in an *ex vivo* checkerboard format with Cry protein combinations to study how they interact. We are further investigating the impact of domain swapping on anthelmintic Cry protein activity and how Cry proteins combine with small molecule anthelmintics. Here, we present these data and discuss how they will collectively impact the development of Cry-based anthelmintics with broad and potent spectrum of activity.

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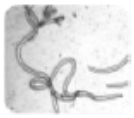

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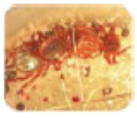

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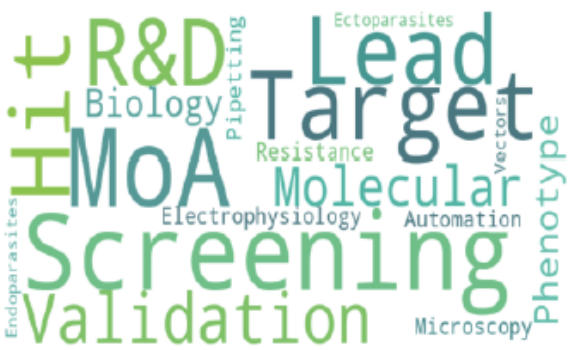

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P1

Towards nucleoside analogues with potent activity against *Trypanosoma* and *Leishmania* species

Hamed Eid A. Alkhalaf,[1] Ehab Kotb Elmahallawy,[2] Marzuq A. Ungogo,[1] Reeshma Sri Sravya Ganivade,[1] Mustafa M. Aldfer,[1] Aleksandar Cvetkovski,[3] Alfonso T. García-Sosa,[4] Hattan S. Gattan,[5] Serge van Calenbergh[6] and Harry P. de Koning[1]

[1]School of Infection and Immunity, University of Glasgow, Glasgow UK; [2]The Roslin Institute, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Edinburgh, UK; [3]Faculty of Medical Science, University "Goce Delcev", Stip, Republic of Macedonia; [4]Institute of Chemistry, University of Tartu, Tartu, Estonia; [5]King Abdulaziz University, Jeddah, Saudi Arabia; [6]Laboratory for Medicinal Chemistry, University of Ghent, Ghent, Belgium.

E-mail: 2932662a@student.gla.ac.uk

One of the main barriers between the identification of potential lead compounds against parasite-borne diseases and their clinical development as potential new drugs is that the development cost for a possible drug against a single neglected disease is deemed to be too high relative to the potential benefits for the manufacturer. Adenosine analogues with potent activity against veterinary trypanosomiasis have been identified [1–3], but most are much less active against *Leishmania* species. We reasoned that the most likely reasons for the uneven activity were (a) differences in activation by adenosine kinase (AK) or (b) differences in adenosine transporters, which are NT1 in *Leishmania* and P1 and P2/TbAT1 in *Trypanosoma brucei brucei* [2,4].

We have created a number of investigative cell lines, including *L. mexicana* ΔLmexAK, and ΔLmexAK expressing TbbAK to investigate whether *Leishmania* AK could be the factor limiting sensitivity to adenosine analogues. Equally, we created ΔLmexNT1 (*null* adenosine uptake) and *T. brucei* ΔTbAT1 as well as ΔLmexNT1 expressing *T. congolense* and *T. vivax* P1-type adenosine transporters. The SAR of the AKs were investigated by determining the EC_{50} values for adenosine analogues against the various cell lines, transporters and AKs. Docking studies were conducted comparing the poses of analogues in the *Leishmania* and *Trypanosoma* adenosine kinases. Detailed transport assays of nucleoside analogues as inhibitors of LmexNT1 are being conducted.

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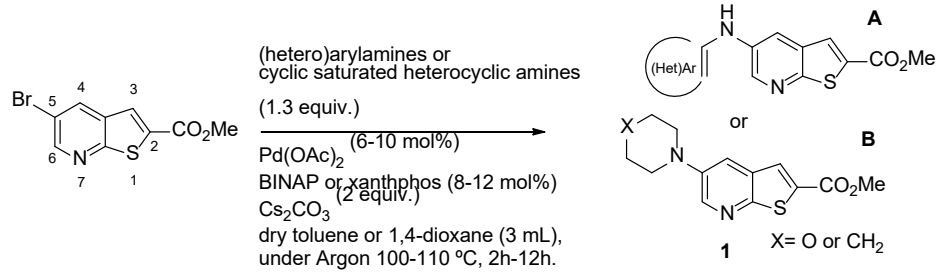
P2

Synthesis of (hetero)aryl and alkylaminothieno[2,3-*b*]pyridines, antiparasitic evaluation and SARs studies

Francisco Ribeiro[1], Juliana P. Sousa[1], Nuno Santarém[2], Anabela Cordeiro-da-Silva[2,3], Maria-João R.P. Queiroz [1]

[1]Centre of Chemistry (CQ-UM), University of Minho, Gualtar, 4710-057 Braga, Portugal
[2] Host-Parasite Interactions, IBMC/I3S, Rua Alfredo Allen, 208, 4200-135 Porto, Portugal
[3] Laboratório de Microbiologia, Departamento de Ciências Biológicas, Faculdade de Farmácia, Universidade do Porto, Portugal
E-mail: mjrpq@quimica.uminho.pt

Thieno[2,3-*b*]pyridine derivatives are of particular interest due to their biological properties, including anti-inflammatory, antiparasitic, antiviral, antifungal, and antidiabetic activities [1]. In this work, we describe the synthesis of new 5-(hetero)aryl and alkylaminothieno[2,3-*b*]pyridines **1** in good to high yields using a Buchwald–Hartwig coupling of methyl 5-bromothieno[2,3-*b*]pyridine-2-carboxylate with aniline derivatives and heteroarylamines (Scheme 1A), or saturated heterocyclic amines (Scheme 1B).



Scheme 1A and B. Synthesis of methyl 5-(hetero)aryl or alkylaminothieno[2,3-*b*]pyridines

The antiparasitic activity of amines **1** was evaluated against *Trypanosoma brucei* and *Leishmania infantum* promastigotes, as well as intracellular amastigotes. Cytotoxicity was assessed in PMA-differentiated THP-1 cells using the MTT assay. Structure-activity relationships (SARs) were identified and will be discussed. The most promising compounds presented IC_{50} values below 10 μM and no significant cytotoxicity (CC_{50} > 100 μM), highlighting them as promising lead candidates.

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P3

Evaluation of antileishmanial and antimalarial activities of endoperoxide analogs derived from marine natural products

Lukas Montejo[1,2], Estelle Messe,[1] Nicolas Jamey,[1] Mansour Dolé Kerim,[1] Laurent Evanno,[1] Isabelle Florent[2], Laurent Ferrié,[1] Sébastien Pomel[1]

[1]Université Paris-Saclay, CNRS, BioCIS, 91400, France.

[2]UMR 7245, Muséum National d'Histoire Naturelle, CNRS, Sorbonne Universités, 75005, Paris, France.

sebastien.pomel@universite-paris-saclay.fr

Malaria and leishmaniasis are both tropical parasitic diseases caused by *Plasmodium* and *Leishmania*, respectively. Recent epidemiological reports revealed about 282 million cases and 610,000 deaths from malaria and about 1 million annual cases for leishmaniasis [1-2]. Treatment of leishmaniasis is limited to only a few available remedies that face issues of toxicity and resistance [3]. Therefore, the development of new, nontoxic, and inexpensive antileishmanials is a priority. Endoperoxides are effective against *Plasmodium*, as evidenced by the continual usage of artemisinins as frontline treatments for both uncomplicated and severe malaria [4]. Plakortin is a natural endoperoxide isolated from the marine sponge *Plakortis halichondrioides* [5]. Thus far, several marine 1,2-dioxane carboxylates have shown interesting antiparasitic activity against both *Plasmodium* and *Leishmania* [6-7]. In this project, 13 unique derivatives of plakortides and mycaperoxides were evaluated for their antiplasmodial and antileishmanial activities *in vitro*. For *Plasmodium falciparum*, the drug resistant FcB1 (to CQ) strain and wild type 3D7 strain were used for *in vitro* assessments. The *in vitro Leishmania* assessments were performed on both axenic and intramacrophagic amastigotes of *Leishmania major*. These compounds were assessed for cytotoxicity on both human AB943 fibroblasts and murine RAW264.7 macrophages. Among the compounds evaluated, LF1440 is the most promising with SI values of >6 in *L. major*, and >85 in *P. falciparum* and should be further investigated.

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P4

Unique actin-like proteins 3 and 5a are essential for *Plasmodium* oocyst formation and development

C. Busse[1], Y. Kobayashi[1], A. Diers[2], A. Binder[3], F. Frischknecht[3] and R. G. Douglas[1]

[1]Institute of Veterinary Physiology and Biochemistry, Justus-Liebig University Giessen, Germany; [2]Institute of Nutritional Science, Justus-Liebig University Giessen, Germany; [3]Integrative Parasitology, Centre for Integrative Infectious Disease Research, Heidelberg University Medical School, Heidelberg, Germany

E-Mail: caroline.susanne.busse@uni-giessen.de

Malaria is a devastating infectious disease caused by *Plasmodium* parasites. The protein dynamics needed for transmission between vertebrate hosts and female *Anopheles* mosquitoes are poorly understood, and understanding the key proteins involved in transmission can unlock additional opportunities for transmission-blocking interventions. Actin-like proteins (Alps) are apicomplexan-specific members of the actin superfamily. The roles of these Alps in the *Plasmodium* progression and transmission are only poorly understood.

In this project, two Alps were characterised in detail. In order to determine their functional relevance, Alp3 and Alp5a knockout (KO) lines were generated in the rodent model *Plasmodium berghei* and subsequently characterised across different life cycle stages. Deletion of either Alp did not affect blood stage growth and gliding motility of ookinetes. However, the Alp3KO line had highly reduced oocyst loads compared to wild type, while sporozoite formation in these oocysts was unaffected. Deletion of Alp5a led to smaller and fewer oocysts as well as severely impaired sporozoite formation. Complementation of knockout lines rescued the oocyst phenotypes and thus confirmed the specific contributions of these genes to oocyst development.

These findings suggest that Alp3 and Alp5a are indispensable for oocyst maturation and development. Understanding their molecular mechanisms will provide important information about oocyst biology and the protein dynamics required for parasite transmission to mosquitoes.

P5

Mitochondrially targeted iron chelators as a potential pharmaceutical for protozoan parasites and pathogenic yeast

Eliška Drncová [1], Robert Sutak [1]

[1] Department of Parasitology, Faculty of Science, Charles University, BIOCEV, Vestec 25250, Czech Republic

E-mail: drncovae@natur.cuni.cz

Iron is a micronutrient that is both essential and potentially toxic, making it a promising target for antimicrobial intervention. As part of nutritional immunity, the host restricts iron availability, to inhibit parasitic growth, while the parasites and fungi deploy efficient iron-scavenging strategies. Because mitochondria are the cellular hub of iron metabolism, mitochondrial targeting of iron chelators represents an attractive therapeutic approach.

We evaluated mitochondrially targeted derivatives of the clinically approved iron chelators deferoxamine (DFO) and deferasirox (DFX), generated via conjugation to the lipophilic triphenylphosphonium (TPP) cation. These compounds exhibit potent activity against a broad spectrum of pathogens, including *Trypanosoma* spp., *Toxoplasma gondii*, *Leishmania* spp., *Plasmodium falciparum*, pathogenic yeasts. Both mito-chelators show remarkable selectivity and benefits from prior development as a promising anticancer agent, highlighting opportunities for drug repurposing.

Structure–activity relationship studies and mechanistic analyses demonstrate that mitochondrial accumulation, rather than iron chelation alone, is the primary driver of antimicrobial activity. In both protozoal parasites and pathogenic yeasts, mitochelators disrupt mitochondrial membrane potential with minimal global iron deprivation.

P6

The use of medicinal plants against vector-borne diseases: Evaluation of *in vitro* leishmanicidal activity of the *Chamomile essential oil*

Hafidh Akkari

Laboratory of Parasitology, University of Manouba, National School of Veterinary Medicine of Sidi Thabet, 2020 Sidi Thabet, Tunisia
E-mail: akkari_hafidh@yahoo.fr

According to the World Health Organization, leishmaniasis is considered as a major neglected tropical disease causing an enormous impact on global public health. Available treatments were complicated due to the high resistance, toxicity, and high cost. Therefore, the search for novel sources of anti-leishmania agents is an urgent need. In the present study, an in vitro evaluation of the leishmanicidal activity of the essential oil of Tunisian chamomile (*Matricaria recutita* L.) was carried out. Chamomile essential oil exhibits a good activity on promastigotes forms of *L. amazonensis* and *L. infantum* with a low inhibitory concentration at 50% (IC_{50}) (10.8 ± 1.4 and 10.4 ± 0.6 µg/mL, respectively). Bio-guided fractionation was developed and led to the identification of (-)-α-bisabolol as the most active molecule with low IC_{50} (16.0 ± 1.2 and 9.5 ± 0.1 µg/mL for *L. amazonensis* and *L. infantum*, respectively). This isolated sesquiterpene alcohol was studied for its activity on amastigotes forms (IC_{50} = 5.9 ± 1.2 and 4.8 ± 1.3 µg/mL, respectively) and its cytotoxicity (selectivity indexes (SI) were 5.4 and 6.6, respectively). The obtained results showed that (-)-α-bisabolol was able to activate a programmed cell death process in the promastigote stage of the parasite [1]. It causes phosphatidylserine externalization and membrane damage. Moreover, it decreases the mitochondrial membrane potential and total ATP levels.

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P7

The potential role of nicotinamide on *Leishmania tropica*: An assessment of inhibitory effect, cytokines gene expression and arginase profiling

Razieh Tavakoli Oliaee[1], Iraj Sharifi[1], Mehdi Bamorovat[1], Alireza Keyhani[1], Zahra Babaei[1]

[1] Leishmaniasis Research Center, Kerman University of Medical Sciences, Kerman, Iran
E-mail: iraj.sharifi@yahoo.com

Leishmaniasis represents a major health concern worldwide which has no effective treatment modality. This study aimed to assess the effect of Nicotinamide (NAm) combination on *L. tropica* Inhibition, as well as on cytokines gene expression and arginase (ARG) activity in *L. tropica*-infected macrophages. The leishmanicidal effects of NAm and Glucantime (meglumine antimoniate, MA) alone and in combination (NAm/MA) were evaluated using a colorimetric assay and macrophage model. Additionally, immunomodulatory effects and enzymatic activity were assessed by analyzing Th1 and Th2 cytokines gene expression and ARG level, respectively, in infected macrophages treated with NAm and MA, alone and in combination.

Findings indicated that the NAm/MA combination demonstrated greater inhibitory effects on *L. tropica* promastigotes and amastigotes compared with each drug individually. The results represented increased levels of IFN-γ, IL-12p40 and TNF-α as well as reductions in IL-10 secretion with a dose response effect, especially in the combination group. The NAm/MA combination also showed a significant reduction in the level of ARG activity at all concentrations used compared to each drug individually.

Our results show higher effectiveness of NAm plus MA in reducing parasite growth, promoting immune response and inhibiting ARG level. This combination may be considered as a potential therapeutic regimen for treatment of volunteer patients with anthroponotic cutaneous leishmaniasis (ACL) in future control programs.

P8

Vaccine adjuvants can boost oxfendazole efficacy in the *Litomosoides sigmodontis* filarial rodent model

Hannah R. Wegner[1], Frederic Risch[1,2], Benjamin Lenz[1], Robert A. Shey[1], Martina Fendler[1], Achim Hoerauf[1,2], Marc P. Hübner[1,2]

[1] Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Bonn, Germany

[2] German Center for Infection Research (DZIF), partner site Bonn-Cologne, Bonn, Germany

E-mail: s6hawegn@uni-bonn.de

Infections with filarial nematodes cause debilitating diseases, affecting millions of people worldwide. Drugs currently used for mass drug administration lack a macrofilaricidal (i.e., adult worm killing) effect. Oxfendazole has demonstrated macrofilaricidal efficacy in pre-clinical models, and is currently being tested in a phase-II clinical trial via eWHORM. Previous research has shown oxfendazole efficacy to be dependent on the immune system, and stimulation with IL-5 during oxfendazole treatment to improve treatment outcome.

Using the *Litomosoides sigmodontis* rodent model for filarial infections, we tested combinations of oxfendazole, adjuvants and modified antigens against adult filarial worms and L3 stages in both BALB/c mice and Mongolian gerbils, to determine whether combination treatment allows for shorter treatment regimens.

While three-day oxfendazole monotherapy was insufficient for a reduction of adult worms (24%), combination therapy of three-day oxfendazole with MF59/LsAg (62%) or CpG-ODN1826/LsAg (55%) led to a reduction of adult worm burden similar to a five-day oxfendazole monotherapy (66%). Additionally, the combination treatment led to a near complete absence of microfilariae, a significant reduction of all embryonal stages, boosted efficacy of oxfendazole against infective L3 larvae in mice (91% compared to 81%), and faster microfilariae reduction in gerbils.

The results of our study indicate that combining oxfendazole with adjuvants boost treatment efficacy, which allows shorter treatment regimens that may further support the success of elimination programs.

P9

Exploring *Myrtus communis* as a Plant-Based Anthelmintic for *Haemonchus contortus* and *Heligmosomoides polygyrus*

Essia Sebai[a b], Amel Abidi[a b], Raja Serairi[c], Bochra Ghawari[a], Mokhtar Dhibi[a], Hayet Benyedem[a], Hafidh Akkari[a]

[a] Laboratory of Parasitology, University of Manouba, National School of Veterinary Medicine of Sidi Thabet, 2020, Sidi Thabet, Tunisia; [b] Faculty of Sciences of Tunis, University of Tunis El Manar, 2092 Manar II, Tunis, Tunisia; [c] Laboratoire des Plantes Aromatiques et Medicinales, Centre de Biotechnologie de Borj-Cedria, B.P. 901, 2050, Hammam-Lif, Tunisia

E-mail: essia.sebai@fst.utm.tn

Anthelmintic resistance in grazing livestock systems has been spreading worldwide in prevalence and severity [1]. Therefore, alternative measures including the use of herbal anthelmintic is considered as one of the successful approaches for the control of anthelmintic resistance [2, 3]. In the present report, we describe the chemical constituents of *Myrtus communis* essential oil, its *in vitro* anthelmintic effect against the most pathogenic gastrointestinal parasite of sheep; *Haemonchus contortus* and its *in vivo* anthelmintic potential using an *in vivo* gastrointestinal parasite model of rodents; i.e. *Heligmosomoides polygyrus*. Chromatographic analyzes of the essential oil (EO) extracted from the leaves of M. communis have shown that this oil was composed mainly of a α-pinene (33.59%), eucalyptol (23.85%) and limonene (14.70%). Regarding the in vitro anthelmintic potential, the ovicidal effect was confirmed in an egg hatch inhibition assay at IC50 = 0.7 mg/mL and with 95.83% of immobility of adult worm's after 8 h of exposure to 2 mg/mL of *M. communis* EO. The anthelmintic capacity of *M. communis* EO was also confirmed by *in vivo* assays conducted against the murine parasite *H. polygyrus*. In fact, at 1200 mg/kg bw of *M. communis* EO, a reduction of 99.70% in faecal egg counts was observed after 7 days of oral treatment, together with a 71.12% reduction in total worm counts. Based on the obtained results, *M. communis* EO showed relevant *in vitro* and *in vivo* anthelmintic effects against gastro-intestinal parasites.

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P10

Tannin-free natural products modulate serotonergic, dopaminergic and tubulin associated pathways in *Caenorhabditis elegans* to reveal novel anthelmintic drug targets

M. Rajiur Rahaman Rabbi, N Ahmed, M. Makshuder Rahman Zim, M. Mahfuzur Rahman Sajib, M. Ahmed, B. Chandra Roy and M. Hasanuzzaman Talukder*

Department of Parasitology, Faculty of Veterinary Sciences, Bangladesh Agricultural University, Mymensingh 2202, Bangladesh

E-mail: talukdermhasan@bau.edu.bd

The growing prevalence of target-specific resistance (TSR) and non-target-specific resistance (NTSR) has hindered the bio-discovery of effective anthelmintic leads over recent decades. Existing studies remain confined to basic efficacy tests and conventional extraction methods. This study aimed to evaluate the anthelmintic potency of 19 tannin-free natural products (NPs) through neurotransmission-mediated alterations in *Caenorhabditis elegans*. Anthelmintic activity was assessed via motility (head thrashes, body bends), mortality, egg hatch inhibition (EHI), and expression of *cat-1*, *ser-1*, *dat-1*, and *tba-1* genes.

Eleven plant extracts from *Azadirachta indica*, *Cassia alata*, *Portulaca oleracea*, *Saraca asoca*, *Eleusine indica*, *Persicaria hydropiper*, *Foeniculum vulgare*, *Clerodendrum infortunatum*, *Linum usitatissimum*, *Hibiscus rosa-sinensis*, and *Vitex negundo,* exhibited significant neurobehavioral and developmental impairments. *P. hydropiper* (1 mg/mL) caused the lowest body bending (31 ± 1.7, $p < 0.01$), while *E. indica* reduced head thrashing (66.3 ± 3.0, $p < 0.01$). *L. usitatissimum* showed the highest lethality (87.3 ± 1.8%, $p < 0.01$), with the lowest LD_{50} values for *E. indica* (0.40 mg/mL) and *L. usitatissimum* (0.411 mg/mL). *C. infortunatum* displayed the strongest EHI (97.5 ± 3.0%, $p < 0.01$).

Gene expression analyses revealed down-regulation of dopaminergic and serotonergic pathways, indicating metabolic and reproductive disruption. This pioneering study highlights the neuromodulatory and developmental effects of native plant extracts and identifies promising molecular targets for next-generation anthelmintic drug discovery from natural products.

P11

Ethno-pharmacology and anthelminthic bioactivity of plants used in traditional medicine in Cameroon

Archile Paguem[1,4*], Manchang Kingsley[1], Nancy Ngwasiri[1], Mireille S.N. Dongmo[2], B. Megane Tsemeu Tchongouang[1], Jérôme Vicogne[3], Simone Haeberlein[4]

[1]Department of Veterinary Medicine, Faculty of Agriculture and Veterinary Medicine, The University of Buea, Cameroon; [2]Department of Biochemistry and Molecular Biology, Faculty of Science, University of Buea, Cameroon; [3]Institut de Biologie de Lille, France; Institute of Parasitology, Justus Liebig University Giessen, Giessen, Germany
E-mail: achillepaguem@yahoo.fr

Fascioliasis is one of the most neglected foodborne zoonotic diseases, caused mainly *Fasciola hepatica* and *Fasciola gigantica*. It affects millions of people and causes huge economic loss in livestock industry. Until now, there is no vaccine available, and the limited drugs used over four decades have showed some limitations including drug resistance. This highlights the urgent need for a more sustainable approach and developing new therapies. We have investigated the *in vitro* activities of plants commonly used by traditional healers and livestock breeders against *F. gigantica: Vermonia amygdalina*, *Vermonia colorata*, *Waltheria indica*, *Siacocephalus latifolus*, *Aristolochoa beuatica* and *Cassia occidentalis.* Various concentrations of plant extracts were tested and time-dose dependent inhibition of adult worm motility and eggs production observed, achieving 100% mortality after 24 h. Among the six plants, *V. amygdaline (conc. 100 µg/ml)* and *A. beuatica (conc. 100 µg/ml)* were the most active. Gas chromatography-mass spectrometry (GC-MS) examination of the Bio extracts showed the presence of alkaloids, tannins, flavonoids and glycosides. In both extracts, Kaempferol, Quercetin and Luteolin were identified, which are known protein kinase inhibitors with activity on human cancers cells. In addition, the *in vitro* efficacy of Kaempferol, Quercetin and Luteolin against further trematodes, *Schistosoma mansoni* and *F. hepatica,* demonstrated the anthelminthic potential of these flavonoids. The findings provide scientific support for the Ethno-pharmarmacology use of those plants in the management of trematodiasis and highlight their potential as sources of anthelmintic compounds.

P12

Standardization of culture techniques and evaluation of compounds against *Fasciola hepatica*

Encinas[1], M. A. Villamizar-Monsalve[1], B. Benito-Vidal[1], J. Sánchez-Montejo[1], A. Muro[1], R. Peláez[2], B. Vicente[1], J. López-Abán[1]

[1] Infectious and Tropical Diseases Research Group (e-INTRO), Biomedical Research Institute of Salamanca, Research Centre for Tropical Diseases at the University of Salamanca (IBSAL-CIETUS), Faculty of Pharmacy, University of Salamanca, 37007 Salamanca, Spain.

[2] Laboratory of Organic Chemistry and Pharmaceutics, Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Salamanca, 37007 Salamanca, Spain

*Funded by MCIN/AEI (PID2021-127471OB-I00)

E-mail: jlaban@usal.es

Fasciolosis, a neglected tropical disease (NTD), is mainly caused by the food-borne trematode *Fasciola hepatica*. It affects millions of people worldwide and generates significant economic losses, particularly in ruminants [1]. Fasciolicide treatments are limited, and the emergence of resistance, first reported in Australian sheep in 1995 [2], threatens their efficacy and control. Therefore, developing standardized systems for evaluating new molecules, optimizing culture methods, and performing *in vitro* testing is essential.

Protocols were standardized to optimize the isolation and cultivation of juvenile stages by removing the metacercarial cysts, using bovine bile, and employing RPMI 1640 culture medium supplemented with avian serum. Viability was assessed by optical microscopy, and fasciolicidal activity was evaluated at 10 µM over 72 h, using triclabendazole sulfoxide as a positive control and DMSO as a negative control, thereby refining the *in vitro* evaluation system using established commercial drugs. Ovicidal activity (OA) was evaluated using the egg-hatching test (EDHT), with water as a control.

The newly synthesized antitubulin compounds C1, C2, C7, and C11 exhibit fasciolicidal activity against juveniles, with median lethal concentration (LC_{50}) values ranging from 6.488 to 7.111 µM. Their OA ranged from 62.2% to 86.2%, supporting their suitability for further preclinical evaluation. These findings provide a foundation for future *in vivo* studies and the potential development of novel fasciolicidal therapies.

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P13

A new automated, motility-based screening assay for discovery of compounds with activity against the juvenile stage of *Fasciola hepatica*

Alice Bernal[1,2], Diana S. Gliga[1], Matías Preza[1], Caroline F. Frey[1], Andrew Hemphill[1], Britta Lundström-Stadelmann[1,3], Natalie Wiedemar[1,3]

[1]Institute of Parasitology, Department of Infectious Diseases and Pathobiology, Vetsuisse Faculty, University of Bern. Bern, Switzerland; [2]Graduate School for Cellular and Biomedical Sciences (GCB), University of Bern, Bern, Switzerland; [3]Multidisciplinary Center for Infectious Diseases, University of Bern, Bern, Switzerland.
E-mail: alice.bernal2@unibe.ch

Fasciola hepatica is a trematode of the *Fasciolidae* family responsible for a parasitic liver disease called fasciolosis affecting humans and livestock [1]. Fasciolosis is responsible for substantial economic losses in cattle farming [2] and is classified as a neglected tropical disease by the World Health Organization [3]. As no vaccine is available, control relies on prevention and on drug treatment, particularly with triclabendazole [4]. However, *Fasciola hepatica* became resistant to triclabendazole leading to treatment failure globally [5]. Screening for new therapeutic options is therefore a critical priority.

We developed a semi-automated, standardized screening assay based on motility monitoring of newly excysted juveniles using microscopic live imaging. Dose-response assays were performed at 10 and 40 µM using a panel of ten compounds with known anthelmintic properties, including triclabendazole (EC50: 2.14 µM) and the new *F. hepatica* TRPM channel activator benzamidoquinazolinone (EC50: 0.69 µM). 3 compounds showed particularly strong activity with EC_{50} values in the nanomolar range: the salicylanilide MMV665807 (40 nM), niclosamide (30 nM), and niclosamide ethanolamine (10 nM).

Scanning electron microscopy revealed no major morphological alterations at EC_{50} concentrations, while higher doses induced parasite shrinkage and tegumental damage. Complementary live/dead staining demonstrated that only triclabendazole exhibited parasiticidal activity, whereas other compounds induced paralysis without parasite death within 72 hours. Overall, this assay provides a robust platform for the identification of novel anti-fasciolosis compounds.

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P14

Molecular characterization and therapeutic potential of the transcription factor HNF4 in the liver fluke *Fasciola hepatica*

Erik Wotschel*, Svenja Gramberg*, Lisa Bauer, Patrice Tegni Sontia, Oliver Puckelwaldt, Simone Haeberlein

Institute of Parasitology, Justus Liebig University Giessen

*Shared first authors

Fasciolosis, a food-borne trematode infection caused by the liver fluke *Fasciola hepatica* and related species, poses a threat to human and animal health worldwide. The scarcity of efficacious therapeutic options and the spread of anthelmintic resistance underscores the need for development of novel anthelmintic agents. In order to identify new anthelmintic strategies, it is essential to gain more profound understanding of fluke biology, particularly regarding organ function and organ-specific gene expression.

The present study focuses on genes that exhibit significant expression in the parasite gut, an organ that is vital for the survival of the parasite. The transcription factor HNF4 is a highly conserved regulator of metabolic homeostasis and cellular differentiation of endodermal organs, but its role for the liver fluke biology is still unknown. During our research, we identified an orthologue of HNF4 in the proteome of *F. hepatica*. Utilizing a combination of spatial and single-cell transcriptomes, in conjunction with in-situ hybridization, the localization of hnf4 expression was successfully determined within the gastrodermis of the parasite. A series of functional studies were conducted using RNA interference (RNAi) in immature parasites as well as in newly excysted juveniles (NEJ), and RNA sequencing of immature parasites after RNAi. Additionally, the highest expression of hnf4 was found in immature flukes. These studies revealed that HNF4 was crucial for the maintenance of gut-associated gene expression, particularly genes encoding proteases such as cathepsins and legumain. The RNAi-mediated knockdown of HNF4 resulted in a substantial decline in the viability of the worms *in vitro*, accompanied by a notable disruption in the intestinal structure in immature flukes and NEJs and a decline in the expression of the Legumain Like protease. Treatment with a commercial small molecule inhibitor of HNF4 had similar effects and was also evaluated in adult flukes. Of note, preliminary data indicated that RNAi treatment causes a decrease in the number of proliferating cells near the intestine of immature flukes, suggesting a connection between HNF4 and stem cell activity.

These findings underscore the pivotal function of HNF4 in preserving the intestinal functionality and overall viability of *F. hepatica*. Further investigations into the molecular mechanisms by which this nuclear receptor regulates gut biology may provide new avenues for drug development, targeting key pathways essential for fluke survival.

P15

In vivo efficacy of tubulin inhibitors against *Schistosoma mansoni**

M.A Villamizar-Monsalve[1], I. Encinas1, B. Vicente[1], L. Santos-López[1], M. Gonzalez-Negrín[1], N. Fernández-Ceballos[2], A. Muro1, R. Pelaez[2] and J. López-Abán[1]

[1]Infectious and Tropical Diseases Research Group (e-INTRO), Biomedical Research Institute of Salamanca, Research Centre for Tropical Diseases at the University of Salamanca (IBSAL-CIETUS), Faculty of Pharmacy, University of Salamanca, Salamanca, Spain.

[2]Laboratory of Organic Chemistry and Pharmaceutics, Department of Pharmaceutical Sciences, Faculty of Pharmacy, University of Salamanca, Salamanca, Spain.

*Funded by MCIN/AEI (PID2021-127471OB-I00)

E-mail: mavillamizar@usal.es

Schistosomiasis, a neglected tropical disease affecting over 250 million people worldwide, causes nearly 1.9 million disability-adjusted life years (DALYs) [1]. The standard drug praziquantel (PZQ) is effective against adult worms but has limited activity against juvenile parasites [2], and global treatment coverage remains low at 31.9% [3]. New therapies are therefore needed. This study evaluated the *in vivo* efficacy of three tubulin inhibitors against *Schistosoma mansoni* in a murine infection model.

CD1 mice (n=80) were infected percutaneously with 100 cercariae and treated during prepatent (days 1-3) or patent (days 44-46) infection stages. Compounds were administered intraperitoneally at 100 mg/kg daily for three days, with PZQ (200 mg/kg, orally, 2 days) as a positive control. Efficacy was assessed by worm reduction burden (WRB), egg reduction rate (ERR), and granuloma analysis.

In prepatent infection, C1 achieved 40% intestinal and 31% liver ERR, while C2 showed minimal activity. In patent infection, C2 demonstrated superior efficacy with 74% WRB ($p=0.036$) and 35% liver ERR, whereas C1 achieved 37% intestinal ERR. C3 showed 55% WRB in prepatent infection but was associated with organ adhesions. Granuloma histology and fibrosis assessment also showed differences between treatment groups.

Tubulin inhibitors showed stage-dependent antiparasitic activity via distinct mechanisms. Further studies on oral bioavailability and compound combinations are needed to complement current treatment.

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P16

Pairing-dependently expressed GPCRs as novel therapeutic targets in *Schistosoma mansoni*

Saranya Geetha, Sophie Welsch, Simone Häberlein, Christoph G. Grevelding

Institute of Parasitology, Justus Liebig University Giessen, Germany
E-mail: saranya.geetha@vetmed.uni-giessen.de

Schistosomiasis, caused by the trematode *Schistosoma mansoni*, remains a major neglected tropical disease, with control largely dependent on praziquantel, a drug with stage-limited efficacy and growing concern of resistance. The parasite's unusual reproductive biology, where females require continuous pairing with males for sexual maturation, offers unique opportunities to identify targets that disrupt development and transmission. G protein-coupled receptors (GPCRs) regulate essential physiological processes and represent one of the most druggable protein families. However, their functional roles in schistosomes are poorly understood.

Here, we functionally characterized selected GPCRs that display pairing-dependent expression in female and male *S. mansoni* [1, 2]. To enhance gene silencing, we established a novel two-dsRNA interference (RNAi) strategy that resulted in high knockdown efficiencies (92–99%). Over a 21-day *in vitro* period, RNAi against these GPCRs produced detrimental phenotypes, including abnormal body morphology, tegumental impairment, reduced motility, and the complete loss of egg production. These changes were accompanied by diminished stem-cell proliferation and a pronounced decrease in mature oocytes, indicating disruption of both somatic functions and reproductive capacity.

Our findings demonstrate that specific GPCRs are indispensable for schistosome vitality and reproductive development. These receptors, therefore, represent promising candidates for target-based drug development, with potential relevance for other parasitic flatworms possessing related GPCRs.

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P17

Natural product-driven anthelmintic discovery: Antinematode activity and drug-development prospects of *Terminalia glaucescens* against *Haemonchus contortus*

Ibukun O. Busari

Safety, Health & Environment Unit, School of Science, Engineering & Environment, The University of Salford, Salford M5 4WT, UK.
E-mail: i.o.busari@edu.salford.ac.uk

The rapid emergence of anthelmintic resistance in gastrointestinal nematodes threatens the sustainability of livestock production and emphasises the need to find novel drug leads [1]. Natural products remain a proven reservoir for antiparasitic drug discovery. This study investigates the antinematode potential of *Terminalia glaucescens* leaf, bark, and root methanol extracts against *Haemonchus contortus*, a parasite of economic importance to small ruminants, with a focus on their relevance for drug design and development [2]. Phytochemical profiling revealed abundant tannins, flavonoids, saponins, alkaloids, and phenolics, supporting a chemically diverse bioactive matrix. *In vitro* egg hatch inhibition assays demonstrated concentration- and time-dependent activity, with leaf extracts showing particularly low IC_{50} values (1.07–1.08 µg/mL at 96–144 h), comparable to the reference drug albendazole. Additionally, haemolysis assays indicated negligible cytotoxicity across tested concentrations, suggesting a favourable preliminary safety profile.

Methodological strengths include standardised *in vitro* screening aligned with WAAVP recommendations and parallel cytotoxicity evaluation; however, limitations arise from the exclusive reliance on egg hatch assays and crude extracts, which do not resolve molecular targets or *in vivo* pharmacodynamics. Building on these findings, future work will prioritise bioassay-guided fractionation, structure elucidation of active compounds, target-based screening, and *in vivo* efficacy studies. In summary, *T. glaucescens* represents a promising plant-based natural product for the development of next-generation anthelmintic agents addressing drug resistance.

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First Name	Last Name	Institution
Hafidh	Akkari	National School of Veterinary Medicine of Sidi Thabet, Tunisia
Maxime	Alessandri	Invenesis, Switzerland
Hamed Eid A	Alkhalaf	Universty of Glasgow, UK
Maria Eugenia	Ancarola	University of Bern, Institute of Parasitology, Switzerland
Raffi	Aroian	UMASS Chan Medical School, USA
Biljana	Arsić	University of Niš, Department of Chemistry, Serbia
Alice	Bernal	University of Bern, Institute for Parasitology, Switzerland
Martin	Blume	Robert Koch-Institute, Germany
Walter	Bronkhorst	TropIQ Health Sciences, Netherlands
Caroline	Busse	Justus-Liebig University Giessen, Germany
Guy	Caljon	University of Antwerp, Belgium
Theodora	Calogeropoulou	National Hellenic Research Foundation, Greece
Claude	Charvet	MSD Animal Health Innovation GmbH, Germany
Anabela	Cordeiro-da-Silva	University of Porto, Faculty of Pharmacy, Portugal
Maria Paola	Costi	University of Modena and Reggio Emilia, Italy
Harry	De Koning	University of Glasgow, UK
Koen	Dechering	TropIQ Health Sciences, Netherlands
Eliska	Drncova	Charles University, Czech Republic
Thomas	Duguet	Invenesis, Switzerland
Viktor	Dyachenko	MSD Animal Health Innovation GmbH, Germany
Markus	Engstler	Julius-Maximilians-Universität Würzburg, Germany
Christian	Epe	MSD Animal Health Innovation GmbH, Germany
Hala	Fahs	New York University, USA
Franco H.	Falcone	Justus-Liebig University Giessen, Germany
Jobst	Fischer	University Giessen, Institute of Parasitology, Germany
Natacha	Gaillard	ASTRA Therapeutics, Switzerland
Pierre	Gatel	Elanco Animal Health, Germany
Saranya	Geetha	Justus-Liebig University Giessen, Germany
Thomas	Geurden	Zoetis, Belgium
Christoph G.	Grevelding	Justus-Liebig University Giessen, Germany
Arnold	Grünweller	Philipps University Marburg, Germany
Simone	Haeberlein	University Giessen, Institute of Parasitology, Germany
Steffen	Hahnel	Boehringer Ingelheim Vetmedica GmbH, Germany
John	Harrington	Boehringer Ingelheim Animal Health, USA
Anja	Heckeroth	MSD Animal Health Innovation GmbH, Germany
Sarah	Hendrickx	University of Antwerp, Belgium
Marc	Hübner	University Hospital Bonn, Germany
Manfred	Jung	University of Freiburg, Germany
Annette	Kaiser	Medical Research Center Duisburg-Essen, Germany
Ronald	Kaminsky	ParaConsulting, Germany
Elmira	Khatamsaz	Boehringer Ingelheim Vetmedica GmbH, Germany
Alexander Christian	Kinner	Justus-Liebig University Giessen, Germany
Joachim	Kloehn	University of Geneva, Switzerland
Friederike	Knapp-Lawitzke	Nuvisans ICB, Germany
Daniel	Kulke	Boehringer Ingelheim Vetmedica GmbH, Germany

First Name	Last Name	Institution
Björn	Kunz	University of Bern, Switzerland
Gaelle	Lentini	University of Bern, Switzerland
Sandra	Leverenz	IS Insect Services GmbH, Germany
André	Lopes	University of Minho, Portugal
Julio	López-Abán	Universidad de Salamanca, España
Britta	Lundström-Stadelmann	University of Bern, Institute of Parasitology, Switzerland
Maxime	Madder	Clinglobal, Mauritius
David	Magri	University of Malta, Malta
Richard J.	Marhöfer	Boehringer Ingelheim Vetmedica GmbH, Germany
Makedonka	Mitreva	Washington University School of Medicine, USA
Yovany	Moreno	Boehringer Ingelheim Animal Health, USA
Mudassar	Mughal	Elanco Animal Health, Germany
Felix	Mühlemeyer	Justus-Liebig University Giessen, Germany
Martin	Murphy	ASTRA Therapeutics, Switzerland
Ard	Nijhof	Freie Universität Berlin, Germany
Sandra	Noack	Boehringer Ingelheim Vetmedica GmbH, Germany
Archile	Paguem	University of Buea, Cameroon
Maria Alexandra	Patras	Fraunhofer IME, Germany
Fabio	Poletti	University of Bern, Institute of Parasitology, Switzerland
Sébastien	Pomel	Université Paris-Saclay, France
Maria-João R. P.	Queiroz	Universidade do Minho, Portugal
Frederic	Risch	University Hospital Bonn, Germany
Douglas	Ross	Justus-Liebig University Giessen, Germany
Heinz	Sager	Elanco Animal Health, Switzerland
Till	Schäberle	Justus-Liebig University Giessen, Germany
Thomas J.	Schmidt	University of Muenster, Germany
Carolin	Schneider	MSD Animal Health Innovation GmbH, Germany
Essia	Sebai	National School of Veterinary Medicine of Sidi Thabet, Tunisia
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Ashwani	Sharma	ASTRA Therapeutics, Switzerland
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Daniel	Sojka	Institute of Parasitology, Ceske Budejovice, Czech Republic
Marius	Spohn	Fraunhofer IME, Germany
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Razieh	Tavakoli Oliaee	University Giessen, Institute of Parasitology, Germany
Wesley C.	Van Voorhis	University of Washington, USA
María Alejandra	Villamizar Monsalve	Universidad de Salamanca, España
Denis	Voronin	Systems Genomic Section, LPD, NIAID, NIH, USA
Hannah	Wegner	University Hospital Bonn - IMMIP Parasitology, Germany
Sophie	Welsch	University Giessen, Institute of Parasitology, Germany
Natalie	Wiedemar	University of Bern, Institute for Parasitology, Switzerland
Jana	Witzenrath	University Giessen, Institute of Parasitology, Germany
Erik	Wotschel	Justus-Liebig University Giessen, Germany
Mostafa	Zamanian	University of Wisconsin-Madison, USA
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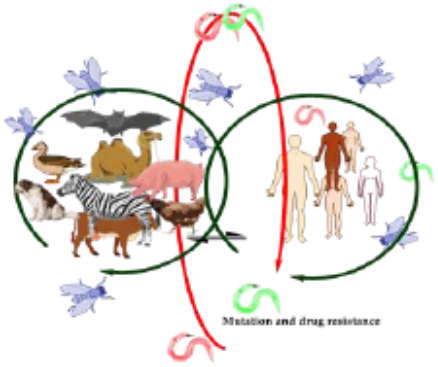

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