Parasitic Helminths : New Perspectives in Biology and Infection

ABSTRACTS

Poster Session 1

Monday 29 August 2022

POSTER SESSION 1: MONDAY 29 AUGUST 6:00 – 8:00 PM

1	**Ayola Akim ADEGNIKA**	Centre de Recherches Médicales de Lambaréné, Gabon	Safety and Efficacy of Praziquantel Treatment for Urogenital Schistosomiasis during Pregnancy preliminary results from a randomized controlled study of the freeBILy project in Lambaréné Gabon
2	**Rowan BANCROFT**	University of Edinburgh	The impact of nutrition and anthelminthic treatment on the gut microbiome in a lab-to-wild model
3	**Sarah BOBARDT**	UC Riverside	The role of endocannabinoids in pulmonary helminth infection
4	**Alice BROWN**	Imperial College London	Extracellular small non-coding RNAs in Trichinella spiralis.
5	**Sujittra CHAIYADET**	Khon Kaen University	Opisthorchis viverrini tetraspanins implicated in extracellular vesicle-mediated host-parasite communication
6	**Ryan CHAN**	McGill University	Elucidating the role of cholesterol in the male- female interplay of Schistosoma mansoni
7	**Alicia CHETTY**	University of Cape Town	Helminth exacerbation of vaginal HSV-2 infection is systemically driven by IL4Ra-independent vaginal eosinophils
8	**Sarah COBB**	University of Texas Southwestern Medical Center	Understanding the basic biology of juvenile schistosomes by studying stem cells
9	**Cécile CROSNIER**	Unversity of York	Investigating host:parasite interactions using a library of recombinant Schistosoma mansoni proteins
10	**Linda DJUNE YEMELI**	University of Yaoundé	Heavily infected loiasis sera contain multiples cross- reactive antigens with varying detection profiles in lymphatic filariasis immunoassays
11	**Faruk DUBE**	Swedish University of Agricultural Sciences	vermectin-induced gene expression changes in adult Parascaris univalens and Caenorhabditis elegans- a comparative approach to study anthelminthic metabolism and resistance in vitro
12	**Annabel FERGUSON**	University of Pennsylvania	Hookworm adaptation to mice lacking Type 2 immune responses
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14	**Jacqueline HELLINGA**	Freie Universität, Berlin	An innovative methodology to perform a long-term evolutionary antiparasitic drug resistance study in the parasite model Caenorhabditis elegans
15	**Martin HORN**	Institute of Organic Chemistry and Biochemistry, Czech Republic	*Schistosoma mansoni* cathepsin C: from functional biochemical analysis to antiparasitic inhibitors
16	**Marc KAETHNER**	Institute of Parasitology, Vetsuisse Faculty	The Achilles' heel of the fox tapeworm? - Investigation of the threonine metabolism of Echinococcus multilocularis
17	**Laura KAMENETSKY**	IBBT Argentina	Parasitic helminth reference genomes
18	**Malcolm KENNEDY**	University of Glasgow	The immunomodulatory IL-13 binding p43 protein of Trichuris muris binds signalling lipids in unusual binding sites
19	**Anna KILDEMOES**	Leiden University Medical Centre	Deciphering response dynamics and functional properties of fucose-specific IgG antibodies induced in schistosomiasis
20	**Andrea LANGELAND**	George Washington University	Identifying differentially expressed genes in permissive and non-permissive hookworm hosts

1 Safety and Efficacy of Praziquantel Treatment for Urogenital Schistosomiasis during Pregnancy : preliminary results from a randomized controlled study of the freeBILy project in Lambaréné Gabon

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Questions: Despite growing evidence of the efficacy and safety of praziquantel (PZQ) during pregnancy and a positive WHO recommendation in 2002, many countries continue to withhold treatment, awaiting further safety data from clinical trials. In fact, there have only been 2 randomised, placebo-controlled trials for the use of PZQ in pregnancy - none of them investigating infection with *S. haematobium*. The question therefore arises whether PZQ is also safe and effective for the treatment of *S. haematobium* in pregnant women.

Aims: As part of the freeBILy-GAB trial, we aimed to evaluate safety of PZQ for urogenital schistosomiasis during pregnancy. We also assessed parasitological efficacy and impact on maternal and newborn morbidity.

Methods: Women were eligible if they were at a gestational age of 16-30 weeks, provided informed consent and were willing to deliver in one of the local maternities. Infection was determined by microscopy and circulating anodic antigen (CAA) using urine. If positive for either test, women were randomized by a 3:1 ratio into two groups (single treatment with PZQ 40mg/kg during pregnancy vs. no treatment during pregnancy). We assessed side effects 1 and 48h after drug intake and collected data on pregnancy outcomes and newborn health status. Efficacy was determined by cure rate (CR) and egg reduction rate (ERR) through urine microscopy filtration after 3 weeks. Morbidity was measured by maternal hemoglobin level at delivery and newborn anthropometric parameters.

Conclusion: Of 607 pregnant women screened, 150 were infected with *S. haematobium,* most infections being of moderate to mild intensity, and 143 were randomized. Drug side effects were all reported as mild to moderate. Mean gestational age and prematurity did not differ significantly between the groups. One case of stillbirth appeared in each cohort, but no relation to the drug was suspected. Efficacy of PZQ resulted into a 85% CR (84.9% vs 55.0%, $p<0.01$) and 95% ERR (0.95[0.91-0.97] vs 0.33[-0.41-0.75]). We found no significant effect of PZQ on maternal hemoglobin levels or anemia, even after controlling for multiple potential confounders, but observed a trend. Likewise, there were no differences in birth weight or prevalence of low birth weight. Impact of treatment on the ongoing pregnancy remains unclear. Nevertheless, we conclude that treatment of urogenital schistosomiasis during pregnancy should not be delayed, as this may lead to increased morbidity in mothers and unborn children.

2 The impact of nutrition and anthelminthic treatment on the gut microbiome in a lab-to-wild model

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The mammalian gastrointestinal tract is a rich ecosystem and focal-point for a wealth of interactions; it is the largest site of the host immune system and diet-derived nutrient absorption, whilst also a preferential niche for helminth parasites and host to the community of microorganisms known as the gut microbiota. Whilst host-nutrition is a key source of intestinal microbiota it also plays a fundamental role in the development of an effective immune response, highlighted by immunodeficiency and increased susceptibility to infection in the malnourished. Moreover, intestinal helminth infections can impair nutrient absorption and compromised immunity can lead to reduced anthelmintic efficacy. To date, the relationship between nutrition, helminth immunity and the gut microbiome has been studied in controlled laboratory models focusing on alterations of specific macro- or micro-nutrients. However, these are unlikely to truly represent findings in natural populations where there is more genetic, ecological, and behavioural variation that can determine exposure and susceptibility to infection, as well as the occurrence of co-infections alongside fluctuations in resource availability due to seasonal shifts which can impact the gut microbiome composition and diversity. We used a high-quality, nutrient-rich diet to experimentally supplement both wild and wild-derived, lab-reared wood mice (*Apodemus sylvaticus)* and measured anthelmintic treatment efficacy and resistance to infection with the gastrointestinal nematode *Heligmosomoides polygyrus.* Previously, we have shown that in both settings, wood mice given this supplemented diet, were more resistant to *H. polygyrus* infection, cleared adult worms more efficiently after treatment and had higher general and parasite-specific immune responses. Here, we expand upon these findings with gut microbiome data from the same study, where we highlight key differences in the diversity and composition of the microbiome between the lab and wild, during infection and determine how supplemented nutrition impacts this – beginning to unravel the mechanisms driving nutrition-induced *H. polygyrus* resistance.

3 The role of endocannabinoids in pulmonary helminth infection

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Abstract: The skin-penetrating nematode *Nippostrongylus brasiliensis* acts as a model of human hookworm infections due to similarities in its lifecycle, such as a mandatory lung stage. In mice, these nematodes cause severe tissue damage in the lung and initiate a strong type 2 immune response. Understanding the protein and lipid signals exchanged between host and helminth will give insight for novel therapeutics to combat the rise of drug resistance to anthelminthics. Here we use gene expression data from individual nematodes at various stages of the lifecycle to discover new pathways that can be targeted. In our previous work, we showed that endocannabinoids (endogenously produced, lipid-derived molecules) are upregulated during the infectious larval stage of the *N. brasiliensis* lifecycle. In mammals, the endocannabinoid system has been shown to have anti-inflammatory effects in the gut, but the role of this system in the lungs has not been well-characterized. We use mice lacking the genes for the mammalian endocannabinoid receptors, Cnr1 and Cnr2, in order to determine the effect of endocannabinoids on the host immune system. We found that macrophages isolated from the *N. brasiliensis*-infected lungs of mice lacking Cnr1, but not Cnr2, had increased Relmα expression, indicating an increase in macrophage alternative activation. Similarly, both lung macrophages and eosinophils from Cnr1-/- mice exhibited excessive binding to *N. brasiliensis* larvae in co-culture. This poster implicates a role for the endocannabinoid system in regulating immune cell-helminth interactions in the lungs and is the premise for the exploration of endocannabinoids as a target to fine-tune immune response to pulmonary helminth infection.

4 **Extracellular small non-coding RNAs in *Trichinella spiralis*.**

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MicroRNAs (miRNA) play important roles inside the cell in post-transcriptional regulation of biological processes and have been found to be secreted by a range of organisms, including parasitic nematodes. It is thought that these extracellular miRNAs may play a role in cell-to-cell, and even parasite-to-cell, communication. However, the mechanism of secretion and selection of miRNAs for export is unclear. In contrast to many examples in the literature describing miRNA secretion within vesicles, the intracellular stage of the parasitic nematode *Trichinella spiralis* has been shown to secrete unencapsulated miRNAs. Questions therefore remain over whether these miRNAs are secreted via direct release or in complex with a chaperone protein, and could this chaperone protein offer some form of stability in the absence of any vesicular membrane? This work explores the secretome of *T. spiralis* and identifies proteins which may be involved in the export and transport of extracellular miRNA. These findings give insight into the suggested role of parasitic miRNAs in manipulating host environments as well as in the wider context of the role of extracellular small non-coding RNAs in various physiological and pathological processes.

5 ***Opisthorchis viverrini* tetraspanins implicated in extracellular vesicle-mediated host-parasite communication**

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Infection with the liver fluke, *Opisthorchis viverrini* remains a public health problem in Southeast Asia and is the major risk factor for bile duct cancer, or cholangiocarcinoma. Adult fluke excretory/secretory products have been well characterized at the proteome level, and contain soluble proteins as well as extracellular vesicles (*Ov*EVs). *Ov*EVs are internalized by bile duct epithelial cells where the adult flukes reside, and contain various proteins and microRNAs that are thought to promote a tumourigenic microenvironment by driving cell proliferation and inflammatory cytokine secretion. To date, the specific mechanisms by which *Ov*EVs are internalized by host cells is unknown. *Ov*EVs are enriched in four-transmembrane spanning proteins called tetraspanins, including two CD63-like tetraspanins (*Ov*-TSP-2 and TSP-3) which appear to be suitable surface markers for *Ov*EVs. Here we investigated the molecular content of *Ov*EVs, the mechanism of internalization into the host cell, and the potential of *Ov*-TSP-2 and TSP-3 in this process. Different endocytosis pathway inhibitors, including clathrin-mediated endocytosis which requires ligand-receptor binding reduced EV internalization and suppressed EV-induced cell proliferation. The co-incubation of *Ov*EVs with antibodies against recombinant *Ov*-TSP-2 and -TSP-3 also prevented *Ov*EV uptake. Finally, RNA interference targeting *Ov-tsp-2* and *tsp-3* genes in adult flukes resulted in substantial malformation of the tegument and secretion of fewer EVs compared to control parasites. Moreover, those EVs that were secreted by dsRNA-treated flukes were deficient in *Ov*-TSP-2 or -TSP-3 proteins, and not efficiently internalized by cholangiocyte. Furthermore, vaccination of hamsters with adjuvanted *Ov*EVs reduced worm recovery after challenge, and passive immunization with a monoclonal antibody against *Ov*-TSP-2 reduced worm and egg burdens by 74% and 67%, respectively. The findings suggest a role for *O. viverrini* tetraspanins in EV-mediated host-parasite communication and further emphasize their importance as subunit vaccines against a range of parasitic helminth infections of humans.

6 Elucidating the role of cholesterol in the male-female interplay of *Schistosoma mansoni*

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Schistosomiasis is a parasitic disease caused by schistosomes which affect over 240 million people worldwide. Schistosomes have separate sexes and are unique in that adult worms always live pair together resulting in egg production, which is responsible for the pathology of the disease. The treatment relies on the mass drug administration of a single drug, Praziquantel, which raises concerns about drug resistance. Therefore, it is urgent to identify novel molecules that can be targeted in alternative therapies. Understanding the reproductive biology of schistosomes will contribute to identify such molecules. The male/female pairing is essential to the sexual maturation of the female, but the signals involved in this pairing remains unknown. Schistosomes are unable to synthesize cholesterol; however male and female worms have been shown to exchange exogenous cholesterol suggesting that they may exploit the host cholesterol for their reproduction. Our research focuses on the role of cholesterol on the reproduction and survival of the parasite. We are characterizing schistosome proteins that interact with cholesterol *in vivo* using RNA interference gene expression on adult schistosomes and immature schistosomula. We are identifying potential signaling pathways that may be regulated by cholesterol by analyzing the effect of cholesterol on gene expression in schistosomes using RNA sequencing. Lastly, we are identifying novel schistosome proteins that interact with cholesterol in *S. mansoni* using a fluorescent cholesterol analogue and quantitative mass spectrometry. This project will contribute to a better understanding of the biology of schistosomes as well as any other parasitic worms that may exploit cholesterol and ultimately, to provide insight into finding new targets and developing novel anthelmintics to combat schistosomiasis.

7 Helminth exacerbation of vaginal HSV-2 infection is systemically driven by IL4Ra-independent vaginal eosinophils

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Parasitic worm infections induce a host immune response that is strongly Type 2 biased. This immune response also influences sites in the body not colonised by the parasite. These systemic effects have been shown to have bystander influences on unrelated diseases such as allergy and autoimmunity in these uncolonized sites. Here, we show that these systemic changes to host immunity are striking in the vagina and have important consequences for a subsequent vaginal herpes simplex virus type II (HSV-2) infection. Following *Nippostrongylus brasiliensis* (Nb) infection, which transits the respiratory and gastrointestinal tracts, we found in the vagina a clear and persistent Type 2 immune imprinting *in vivo*. Nb infection resulted in the induction of a number of typical type 2 signature responses, which included increased detection of the alarmin IL-33, type 2 cytokines IL-4 and IL-5 in vaginal tissue and lavages. Associated with this were raised and long-lasting vaginal eosinophil populations. Nb infection also resulted in exacerbated genital pathology and inflammation, following subsequent intravaginal HSV-2 infection. Increased HSV-2 pathology in mice with prior helminth exposure associated with reduced type 1 immunity and increased IL-33, ILC2 and IL-5 responses, as well as significant vaginal eosinophil accumulation, with no effect on viral shedding. Increased HSV-2 immunopathology was independent of canonical Th2 immune signalling via IL-4Ralpha. Here, we found equivalent Nb-induced exacerbation of HSV-2 pathology between WT and IL-4Ra$^{-/-}$ mice, which associated with increased genital eosinophil populations. Disruption of IL-33 signalling with HpARi and infection of dblGATA$^{-/-}$ and Siglec-F-depleted mice demonstrated that Nb-induced exacerbation of HSV2 pathology was a result of an IL-33, ILC2, IL-5, eosinophil self-promoting immune cycle in the vagina. We have therefore identified that helminth infections can induce a striking disruption to immunity in the vaginal mucosa, which enhanced immunopathology to a sexually transmitted viral infection.

8 Understanding the basic biology of juvenile schistosomes by studying stem cells

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Schistosomiasis afflicts over 240 million people, killing hundreds of thousands every year and causing socioeconomic damage rivaling malaria. Schistosomes, the causative agent, are parasitic flatworms with a complex two-host life cycle. Treatment relies upon a single drug, praziquantel (PZQ), that has significant drawbacks including a lack of efficacy against juvenile parasites. Indeed, the insensitivity of juvenile worms to PZQ is thought to be a major contributor to the limited efficacy of PZQ in the field. It is unclear why juvenile parasites are refractory to PZQ. The drug causes tissue damage in both juvenile and adult animals and this damage can be at least partially repaired *in vitro*. One potential explanation for the juvenile's hardiness comes from the observation that juvenile schistosomes have much higher numbers of somatic stem cells (termed "neoblasts") compared to adult parasites. In adult schistosomes, these neoblasts are thought to be required for the parasite's survival in the host by homeostatically maintaining tissues such as the skin and the gut, but their role in the juvenile is less clear. We hypothesize that the increased number of neoblasts in the juveniles allows them to repair PZQ-mediated damage better than adult parasites, leading to the lack of efficacy against juvenile animals. In order to study the role of juvenile neoblasts in praziquantel resistance, we must first improve our understanding of the basic biology of the juvenile parasite. To this end, we are employing techniques such as single-cell RNAseq, *in situ* hybridization, and EdU-based fate mapping experiments to understand the molecular identity and function of neoblasts in this important stage of the schistosome lifecycle.

9 Investigating host:parasite interactions using a library of recombinant *Schistosoma mansoni* proteins

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Schistosomiasis is a major parasitic disease affecting over 200 million individuals and responsible for an estimated 200,000 deaths annually. Its huge human and socio-economic impact highlight the need for new prophylactic measures against the disease. Despite extensive efforts from the research community, there is currently no licenced vaccine and schistosomiasis control in endemic populations heavily rely on the mass administration of praziquantel, which only targets the adult stage of the parasite. Within a few days of infecting their host, schistosomes enters the vascular system where they will develop and reside throughout their life. To subvert potential attack by the human immune system, schistosomes have developed extensive mechanisms of immune evasion and modulation. Yet, the identity of the parasite proteins and of the human targets involved in these mechanisms remain poorly defined. To investigate schistosome biology, we have recently produced a library of 120 recombinant cell-surface and secreted *Schistosoma mansoni* proteins, which we produce in mammalian cells to promote the formation of conformational epitopes. Comparison of the immunoreactivity of these proteins, either in their native conformation or following heat-treatment, against sera from individuals living in endemic areas demonstrated that the majority contain conformational epitopes. We have used this protein library in the context of controlled human infections to identify early serological markers of infection, and in vaccine challenge studies in a murine model of schistosomiasis. To identify protein:protein interactions involved in immune modulation, we are currently using our recombinant *S. mansoni* proteins to interrogate a collection of over 700 human immune receptors using the AVidity-based Extracellular protein Interaction Screening approach (AVEXIS). We hope the identification of immunomodulatory pathways used by schistosomes will point to new vaccine targets, and more broadly will lead to novel therapeutic avenues in the control of allergic and auto-immune responses.

10 Heavily infected loiasis sera contain multiples cross-reactive antigens with varying detection profiles in lymphatic filariasis immunoassays

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Loiasis cross-reactivity with lymphatic filariasis (LF) rapid tests (RDTs) is a major problem for LF elimination in co-endemic areas, because it makes mapping and monitoring of LF unreliable. Very little is known about the nature of this cross-reactivity. It is more common in individuals with high *Loa loa* microfilariae density (MFD), but not all high MFD individuals test positive to LF-RDT and the presence of *L. loa* circulating filarial antigens (CFA) may be transient in nature. To gain a better understanding of that transient nature of loa CFA and find a representative cross-reactive biomarker that can be used to distinguish true LF from loiasis, we undertook a longitudinal study in Okola health district, Centre Cameroon. 73 LF-RDT positive and 13 LF-RDT negative controls, all with high MFD were enrolled and followed up quarterly for 15-months. At each follow-up, MFD and LF-RDT status were determined, and venous blood was tested to quantify *L. loa* CFA by ELISA. Although the proportion of individuals with loiasis cross-reactivity was relatively constant over time (Chi-square=5.982; df=4; p-value=0.2005), CFA levels significantly decreased between baseline and each follow-up visit (Kruskal-Wallis test: H (4): 10.53; p=0.0324). There was poor agreement between RDT and CFA ELISA results (kappa score ranging from -0.133 to 0.123). Western blots done on baseline and 15-months follow-up samples demonstrated the presence of multiples *L. loa* CFA, including an ~80kDa protein present in most samples at baseline as well as at 15-months. These results together suggest that most heavily infected sera contain multiple *L. loa* CFA, but not all are detectable by RDT. Mass spectrometry (MS) analyses on baseline samples identified two promising biomarkers presenting in >90% of infected samples. MS analyses are ongoing on 15-months samples and will enable us to confirm whether this biomarker is constantly present, and might be used to distinguish true lymphatic filariasis from loiasis.

11 Ivermectin-induced gene expression changes in adult *Parascaris univalens* and *Caenorhabditis elegans*- a comparative approach to study anthelminthic metabolism and resistance *in vitro*

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The nematode *Parascaris univalens* is one of the most prevalent parasitic pathogens infecting horses but anthelmintic resistance undermines treatment approaches. The molecular mechanisms underlying drug activity and resistance remain poorly understood in this parasite since experimental *in vitro* models are lacking. The aim of this study was to evaluate the use of *Caenorhabditis elegans* as a model for *P. univalens* drug metabolism/resistance studies by a comparative gene expression approach after *in vitro* exposure to the anthelmintic drug ivermectin (IVM). Twelve adult *P. univalens* worms in groups of three were exposed to ivermectin (IVM, 10^{-13} M, 10^{-11} M, 10^{-9} M) or left unexposed for 24 h at 37 °C, and total RNA, extracted from the anterior end of the worms, were sequenced on Illumina NovaSeq. Differentially expressed genes (DEGs) involved in metabolism, transportation, or gene expression with annotated *Caernorhabditis elegans* orthologues, were identified as candidate genes to be involved in IVM metabolism/resistance. Similarly, groups of 300 adult *C. elegans* worms were exposed to IVM (10^{-9} M, 10^{-8} M and 10^{-7} M) or left unexposed for 4 h at 20 °C. Quantitative RT-PCR of RNA extracted from the *C. elegans* worm pools was used to compare against the expression of selected *P. univalens* candidate genes after drug treatment. Adult P. univalens worms had 1085 DEGs after IVM exposure, however the relative gene expression changes were small and there was large variability amongst worms. After comparative bioinformatics analyses, 15 DEGs were chosen as candidate genes for C*. elegans* characterization. Candidate genes, including the putative drug target *lgc-37,* responded to IVM in *P. univalens*, but marginal to no responses were observed in *C. elegans* despite dose-dependent behavioral effects observed in *C. elegans* after IVM exposure. Thus, the overlap in IVM induced gene expression in this small set of genes was minor in adult worms of the two nematode species. This is the first time a comparative gene expression approach has evaluated *C. elegans* as a model to understand IVM metabolism/resistance in *P. univalens*. Genes in *P. univalens* adults that responded to IVM treatment were identified. However, identifying conserved genes in *P. univalens* and *C. elegans* involved in IVM metabolism/resistance by comparing gene expression of candidate genes proved challenging. The approach appears promising but was limited by the number of genes studied (n=15). Future research comparing more genes between the two species may uncover new candidate genes implicated in drug metabolism and/or resistance.

12 **Hookworm adaptation to mice lacking Type 2 immune responses**

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Hookworms cause morbidity in humans and animals across the globe. The rising incidence of anthelmintic resistance and lack effective vaccines makes it imperative to generate new avenues for therapeutic intervention. Most infections are recurrent and hookworm burdens increase with host age in endemic regions, implying that hookworms adapt to host immune selective pressure. Interleukins 4 and 13 are central to host protective immunity against the rat hookworm *Nippostrongylus brasiliensis* (*Nb*). IL-4 and IL-13 signaling requires expression of the prototypical Type 2 transcription factor, signal transducer and activator of transcription 6 (STAT6) that drives expulsion and killing of worms through hematopoietic (TH2 cells, ILC2, M2 macrophages) and non-hematopoietic cells (Tuft cells, goblet cells, smooth muscle). This study addresses whether hookworms' transcriptome is changed by the lack of type 2 immune pressures in STAT6 deficient hosts and if this attenuates parasite fitness in a wildtype host. We have assessed parasite fitness through quantification of eggs per gram of host feces (EPG), adult parasite hemoglobin levels, and individual adult parasite egg output. Data show that *Nb* shows improved fitness within STAT6 KO mice but when STAT6 KO adapted worms are introduced into WT mice, they show attenuated fitness. This altered fitness phenotype of STAT6 KO adapted parasites is reflected by a significant change in parasite transcriptional profile. Specifically, 7 transcripts are significantly up-regulated and 8 are down-regulated in STAT6 KO adapted parasites relative to WT lines. The most up-regulated transcript encodes a cysteine-rich/antigen 5/pathogenesis-related 1 CAP-family domain containing protein (9.3 log2 fold-change) implicated in hemoglobin degradation. Collectively, this suggests that hookworms adapt to host immune pressure, which if lost, results in parasites with higher reproduction and feeding capacity, but greater immunogenicity. The mechanistic nature the adaptive change observed is under current investigation.

13 **Role of nuclear hormone receptors in connecting drug resistance, development and lipid metabolism in nematodes**

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The nuclear hormone receptor NHR-8 triggers the protective response to drug exposure and it has recently emerged as an important factor of ivermectin resistance in *Caenorhabditis elegans* and in the parasitic nematode of ruminants *Haemonchus contortus*. Besides, NHR-8 stands as a prominent regulator of lipid homeostasis in *C. elegans*, highly expressed in the intestine, where it regulates genes encoding transporters or enzymes involved in the utilization of cholesterol and fatty acids, on which nematodes are fully dependent for their reproduction and survival. NHR-8 also controls the synthesis of steroid ligands of DAF-12, another NHR which controls the development of infectious parasites. In order to understand the connecting role of NHR-8 in drug resistance, worm development and lipid metabolism, we compared the lipid status of different *C. elegans* strains: Wild-type; IVM-resistant experimentally selected on drug pressure in our laboratory, and NHR-8-deficient worms (Obtained in *C. elegans* Genetic center). We quantified lipids by GC-MS, and visualized the lipid content and fat mobilization in living animals by Coherent Anti-strokes Raman spectroscopy (CARS) confocal imaging. The phenotypic changes in lipid content observed in IVM resistant worms and in NHR-8 deficient animals were analyzed on the light of transcriptomic data in *C. elegans*, comparing the expression of relevant genes in the different strains. The relationship between changes in gene expression and lipid content in *C. elegans* exposed to stress conditions (starvation or drug) will provide insight into how NHR-8 influences lipid storage and energy mobilization as a function of resistance status. By deciphering such metabolic connection, we'll open new way to find novel targets to undermine resistant worms, and markers for IVM-resistant worms.

14 An innovative methodology to perform a long-term evolutionary antiparasitic drug resistance study in the parasite model *Caenorhabditis elegans*

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Free living nematodes such as *Caenorhabditis elegans* (*C. elegans*) are an appealing tool for experimental evolution given the easiness of working with them in cultured laboratory conditions. *C. elegans* are also a critical model for parasitic nematodes in working with antiparasitic drugs, from understanding current and new drugs' molecular mechanisms to uncovering more drug targets. This is critical to counter the increase in antiparasitic drug resistance. However, the research of antiparasitic drugs with *C. elegans* has stalled due to the lack of nematode media resources to evenly distribute these drugs to the population. We present a new methodology for studying the impact of antiparasitic drugs in *C. elegans* for long-term evolutionary studies. Our viscous medium (V medium) was initially designed for *C. elegans* maintenance during long-term evolution experiments and high-throughput assays. V medium provides a less structured environment than the standard nematode growth media. Nevertheless, it offers the worm population enough support to move freely, mate, and reproduce at a rate comparable to standard agar cultures. Here we have adapted the V medium for use in antiparasitic research. We have performed an evolutionary development experiment designed to study ivermectin resistance progression in different populations. The observed development of drug resistance for each population size was consistent with its mathematical modelling predictions. We also observed a sensitivity difference of each population size to ivermectin drugs in vitro phenotypic assays. We believe that using the V medium in *C. elegans* drug studies will dramatically improve antiparasitic resistance research, and our study is one of the first multidisciplinary evolutionary projects.

***15* *Schistosoma mansoni* cathepsin C: from functional biochemical analysis to antiparasitic inhibitors**

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Blood flukes of the genus *Schistosoma* cause schistosomiasis, a neglected parasitic disease that affects over 200 million people. Treatment relies on just one drug, and new therapies are needed. Our work is focused on the cysteine protease cathepsin C from *Schistosoma mansoni* (SmCC), which is involved in digestion of host hemoglobin, the most important source of nutrients. We demonstrated using functional proteomics that SmCC is present in blood-dwelling developmental stages of *S. mansoni* infecting humans (eggs, schistosomula, and adults). Gut association of SmCC in adult parasites was shown by immunofluorescence microscopy. Further, we investigated regulation of SmCC activity by synthetic inhibitors. A library of peptidomimetics with a reactive tetrafluorophenoxymethyl ketone warhead was tested in a kinetic fluorescence assay against native and recombinant SmCC. The most potent inhibitors of SmCC activity were able to induce deleterious phenotypes in cultured schistosomes. Our results suggest that SmCC is a promising target for the treatment of schistosomiasis and SmCC inhibitors represent potential anti-schistosomal drugs.

16 **The Achilles' heel of the fox tapeworm? - Investigation of the threonine metabolism of *Echinococcus multilocularis***

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Alveolar echinococcosis (AE) is a severe zoonotic disease caused by the metacestode of the fox tapeworm *Echinococcus multilocularis*. Novel treatment options against AE are urgently needed. *In vitro* experiments showed strong scavenging of threonine by *E. multilocularis* metacestodes. We thus aim to elucidate the threonine metabolism of *E. multilocularis* with a specific focus on threonine dehydrogenase (TDH), an enzyme that is actively expressed in *E. multilocularis* metacestodes. EmTDH is potentially a future drug target against AE, as human TDH is a non-functional pseudogene. In this study, $^{13}C_4$ L-threonine and its metabolites were traced in *in vitro* cultured metacestodes to give new insights into how threonine is metabolized in *E. multilocularis*. The flux analysis with $^{13}C_4$ L-threonine showed that *E. multilocularis* metacestodes take up threonine and metabolize it to glycine. In addition, threonine may be used for the biosynthesis of glutathione. In addition, we study the effect of L-threonine on the growth of *in vitro* cultured metacestodes via a newly established growth assay applying an automated script in ImageJ and on the proliferation of *E. multilocularis* stem cells. Growth assays showed significant increase in diameter of threonine-treated metacestodes. Flux analysis and growth assays provided evidence that threonine metabolism is important for *E. multilocularis* and inhibiting this metabolism could provide new treatment options. Quinazoline carboxamids (Qc) are potent inhibitors of mouse TDH and we aim to test them against *E. multilocularis*. Qcs will be tested in organism-based and target-based screening approaches against recEmTDH and recMmTDH. These experiments will show whether Qcs can inhibit the threonine metabolism in *E. multilocularis* and whether they might provide interesting candidates for future treatment

17 **Parasitic helminth reference genomes**

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Whole genome sequences provide extraordinary information about any organism. Despite the global impact, both medically and economically of helminthic infections these parasite genomes are underrepresented in genomic databases. The first genome sequence from a parasitic helminth was published in 2007, since then only ~200 genomes are available most of them being draft assemblies. Our work centers in complete genome sequencing of neglected parasitic helminthes. Recently, we sequenced the complete genome of *Echinococcus canadensis* (G7) and compared it with *Echinococcus multilocularis and Echinococcus granulosus* (G1) genomes. Comparative genomics allowed us to confirm the status of *E. canadensis* (G7) as a separate species and demonstrated a high nucleotide sequences divergence in relation to *E. granulosus* (G1). This result was unexpected since both parasite species are considered to belong to the same species complex: *Echinococcus granulosus sensu lato*. At present there is no unequivocal taxonomic classification of *Echinococcus* species therefore additional Cestode genomes are needed to be sequenced. In this regard, we sequence *Echinococcus oligarthrus* genome to and reconstruct *Echinococcus* phylogeny by whole genome SNPs analysis. Also, in an international consortium we are sequencing *Echinococcus vogeli* and re sequencing *Echinococcus* spp. form several host and geographical regions. Moreover, we are also sequencing the genome of the giant kidney worm *Dioctophyma renale,* the largest parasitic nematode of terrestrial vertebrates described so far which affects domestic animals, endangered wildlife, and humans. With this foundational project we aimed to obtain complete information about Clade I nematodes which is the least studied group of this phylum.

18 The immunomodulatory IL-13 binding p43 protein of *Trichuris muris* binds signalling lipids in unusual binding sites

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The p43 protein of *Trichuris muris* contributes more than 95% of the protein secreted by adult worms, is non-immunogenic in infection in mice, has IL-13 and glycan-binding activities that likely underpin chronic intestinal infection, and is demonstrably immunomodulatory. The X-ray crystal structure of p43 reveals extensive surface-connected internal cavities that vary in the charge characteristics of their walls, suggesting binding sites specific for different types of apolar ligand. Using a competitive fluorescence-based approach, we found that p43 binds fatty acids and a range of other lipids, such as retinol, and some pharmacologically-active lipids and their precursors. There is, however, selectivity in the binding of structurally similar lipids. For instance, while arachidonic acid (precursor to prostaglandins and leukotrienes) binds to p43, the structurally similar neurotransmitter anandamide binds in only a subset of arachidonic acid-binding sites. Comparing the amino acid sequences of p43 with orthologues among other Clade I nematodes including the giant kidney worm, *Dioctophyme renale,* and *Trichinella spiralis* reveals sections that are highly conserved, interrupted by sections that are highly divergent. Mapping the divergent regions onto the structure of p43 reveals potential differences in surface-connected cavities within the protein and areas on the protein's surface that are potentially involved in external interactions. p43 and its orthologues are the result of an ancient duplication and the internal cavities in its two domains have diverged in shape and charge distributions, thereby presumably increasing its binding repertoire. p43-type proteins only occur in Clade I nematodes (Dorylaimia), in which the other nematode-specific lipid transporter proteins present in all the other clades (the NPAs and FARs) are absent. Combining an understanding of the 3D structure of p43 with its lipid binding may reveal whether its lipid-binding adds to its immunomodulatory activities by delivering or sequestering signalling lipids. To this end we are also engaged in metabolomic analysis of ligands that are naturally bound to worm-derived p43.

19 Deciphering response dynamics and functional properties of fucose-specific IgG antibodies induced in schistosomiasis

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Schistosome infection induces a plethora of antibodies recognising a wide range of antigens expressed by parasite larvae, adult worms and eggs. A large proportion of these antibodies are specific for antigenic glycans that are part of the parasite's glycoprotein and glycolipid repertoire. The role of these anti-glycan antibodies in immunity remains poorly understood. They likely contribute to protective immunity and immunomodulation, but may also cause smokescreen or cross-reactive effects. Extensive glycomics work has shown that schistosomes contain several unique glycan elements. Particularly, the wide range of fucosylated glycans antigens in schistosomes elicit high antibody titres in humans. Here we firstly focus on elucidating response dynamics of IgG antibodies specific for defined fucosylated glycan elements, which are highly expressed particularly in cercariae and eggs. Longitudinal response dynamics are obtained from two primary controlled human *S. mansoni* infection models and two schistosomiasis endemic area cohorts. Total and subclass IgG antibody profiles were measured by custom glycan microarray analyses. Secondly, we focus on functional properties of antibodies recognising representative synthetic Fuc(α1-3)GalNAc and Fuc(α1-2)Fuc(α1-3)GalNAc elements conjugated to microbeads. To determine Fc-region effector functions, these synthetic glycan:bead complexes are used in functional assays such as determination of antibody dependent complement deposition, NK cell activation and monocyte phagocytic capacity. By comparing antibody properties from primary infections and chronic infections, we aim to gain understanding of these fucose-specific antibodies in terms of their role in protection or susceptibility to schistosome infection. Such knowledge is essential to determine whether these fucose-specific antibodies are involved in acquired partial immunity to schistosomiasis as well as progress toward identification of correlates of protection, and hence future vaccine development advances.

20 Identifying differentially expressed genes in permissive and non-permissive hookworm hosts

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Hookworm infection is a devastating disease affecting approximately 500 million people worldwide, and is particularly harmful in children and women. Disease caused by the blood-feeding worm in the intestine can lead to anemia as well as retarded physical and intellectual growth. The current control strategy is mass drug administration (MDA) using anthelmintics. This approach is prone to rapid reinfection, necessitating treatment on an annual or biannual schedule. The discovery of anthelmintic resistance in livestock and companion animals has caused an urgent need for new drug treatments. The molecular mechanisms that determine host specificity are poorly understood. Parasites can range from strict specialists able to infect only closely related host taxa, to generalists who can infect several unrelated species. Hookworms offer a gradient across this spectrum, from *Necator americanus* which can only successfully infect humans, to *Ancylostoma ceylanicum* that can infect carnivores, humans, and hamsters. Better understanding of the determinants of host specificity would provide insights into potential control mechanisms. Using RNAseq, we examined differentially expressed genes (DEGs) in permissive (hamster) and non-permissive (mouse) hosts at different timepoints during infection with *A. ceylanicum.* Analysis of the data has identified candidate genes for immune responses in mice, as well as potential permissive signals in hamsters. Specifically, immune pathways associated with resistance to infection are upregulated in a non-permissive host, possibly providing a protection mechanism that does not exist in a permissive host. Additionally, hypotheses-driven analysis identified genes that may inform the hookworm that it has invaded a permissive host. These data provide insight into the gene expression differences between a permissive and non-permissive host in response to hookworm infection.