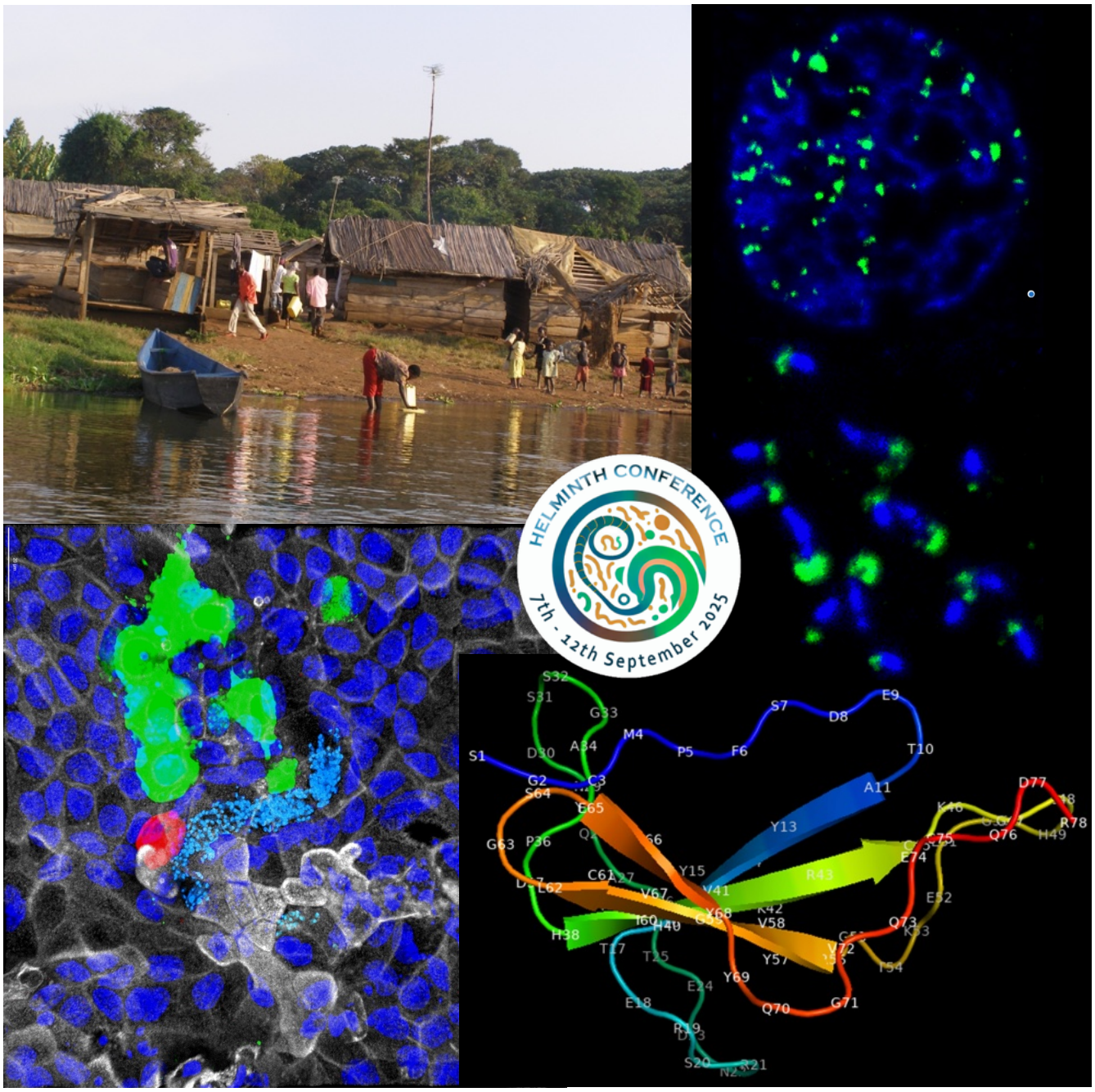
Parasitic Helminths: New Perspectives in Biology and Infection



Hotel Bratsera
Hydra, Greece
7 - 12 September 2025

The Hydra Conference 2025 has been generously supported by:

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Amy Buck (University of Edinburgh, UK)
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Rick Maizels (University of Glasgow, UK)
Murray Selkirk (Imperial College London, UK),

Cover Photos:

Upper Left: *Schistosoma* endemic fishing community, Koome Islands, Uganda (from Alison Elliott, UVRI/LSHTM)

Upper Right: Chromosomes of the root-knot nematode *Meloidogyne incognita* in blue (DAPI staining) with the telomeric repeats in green, with uncondensed chromosomes on the left and condensed chromosomes in metaphase on the right (Image from Evelin Despot-Slade and Nevenka Meštrović (Ruđer Bošković Institute, Zagreb, Croatia).

Lower Left: *Trichuris* whipworm first-stage larvae infecting intestinal epithelial cells in caecaloids. In red, Dclk-1, marker of tuft cells; in green, the lectins UEA and SNA bind mucins in goblet cells; in blue and aqua, DAPI stains nuclei of intestinal epithelial cells and larvae, respectively; and in white, phalloidin binds to F-actin. (Image from Maria A. Duque-Correa, University of Cambridge).

Lower right: *Heligmosomoides polygyrus* Transforming Growth factor β Mimic (TGM) -4, Domain 1 structure (Image from Luke Power, Maizels Lab, University of Glasgow

Parasitic Helminths - New Perspectives in Biology and Infection 7 - 12 September 2025, Hydra, Greece

	Sunday 7 September	Monday 8 September	Tuesday 9 September	Wednesday 10 September	Thursday 11 September	Friday 12 September
	ARRIVE	**Session 1** **Helminth-host Interactions**	**Session 4** **Anthelmintics & Vaccines**	**Session 7** **MINI SYMPOSIUM**	**Session 10** **Neurobiology & Development**	DEPART
9:00		**Elia Tait Wojno**	**Jonathan Marchant**	**Shahid Siddique**	**Aaron Maule**	
9:20						
9:40		Anna Heawood	Petra Matouskova	Unnati Sonawala	Robin Beech	
10:00		Nicole Ong	Amanda Shaver	Vincent Hanlon	Daniel Sprague	
10:20		Daniel Price	Anne Lespine		Albane Le Maire	
10:40-11:10		**Coffee Break**				
		Session 2 **Evolution & Resistance**	**Session 5** **Ecological & Evolutionary Dynamics**	**Session 8** **MINI SYMPOSIUM**	**Session 11** **Co-infection & Disease**	
11:10		Andy Fraser	Maria Yazdanbakhsh	**Etienne Danchin**	Amy Pedersen	
11:30		Manon Mallet	Yoanne Mouwenda		Wiebke Hartmann	
11:50		Inés Guarnaschelli	Anne Jensen	Alison Blundell	Ophélie Piefort	
12:10		Melanie Hannebelle	Simon Babayan	Peter Di Gennaro	Benjamin Dewals	
12:30		Frances Blow	Mohammed Ahmed		Eva Pastille	
12:50 to 16:00			**Afternoon Break**			
		Session 3 **exRNA interactions**	**Session 6** **Helminth-Microbe Interactions**	**Session 9** **Mucosal Interactions**	**Session 12** **Immunity & Modulation**	
16:00		Collette Britton	Rory Doolan	Maria Duque Correa	**Christoph Klose**	
16:20		Cei Abreu-Goodger	Frédéric Fercoq	Hannah Peaty		
16:40		Peter Nejsum	Mark Taylor	Alasdair Nisbet	Sarah Dörken	
17:00	**Registration Opens at Bratsera Hotel**	**Poster Pitches x 17**	Robert Colebunders	**Poster Pitches x 17**	Tiffany Bouchery	
17:20			Nolwenn Dheilly		Ruby White	
18:00		**Poster Session 1**	*17:40 End of Session*	**Poster Session 2**	*17:40 End of Session*	
18:45	**Pre-lecture Drinks**		**Vlychos Taverna Dinner** (Boat leaves 19:00)			
19:45	**Keynote Lecture: Alison Elliott**				**Bratsera Farewell Dinner** (20:30)	
21:00 to late	**Welcome Dinner Bratsera Hotel**	*20:00 End of Session*		*20:00 End of Session*		

Parasitic Helminths – New Perspectives in Biology and Infection

2025 Programme

Sunday 7 September

17:00 Registration Opens, Bratsera Hotel

18:45 Pre-lecture Drinks

19:45 Keynote Lecture, Alison Elliott :

The wonder of worms!
How parasitic helminths can change our lives

21:00 Welcome Dinner, Bratsera Hotel

Keynote Lecture 2023 : Maria Yazdanbakhsh, Leiden University Medical Center

Timings for all presentations include minimum of 5 minutes for discussion.

Monday 8 September

09:00-10:40 Session 1. Helminth-host interactions. Chair: Rick Maizels

09:00	**Elia Tait Wojno**	University of Washington, USA	Prostaglandin regulation of Type 2 inflammation during helminth infection
09:40	Anna Heawood	University of Glasgow, UK	Exploring helminth-derived TGF-β mimics as modulators of inflammatory disease
10:00	Nicole Ong	University of Dundee, UK	The cellular targets and parasite immunomodulation of IL-33 signalling in *Heligmosomoides polygyrus bakeri* infection
10:20	Daniel Price	Moredun Research Institute, UK	Modulation of host epithelia by excretory-secretory products from ovine gastrointestinal parasitic nematodes

10:40 – 11:10 Coffee Break

11:10 – 12:50 Session 2. Evolution and Resistance. Chair: Matt Berriman

11:10	Andy Fraser	University of Toronto, Canada	A new way to see metabolism - smol-seq brings the power of DNA sequencing to metabolomics
11:30	Manon Mallet	University of Montpellier, France	Structural and functional insights into the nuclear receptor DAF-12 from different parasitic nematodes
11:50	Inés Guarnaschelli	University of Uruguay	Cellular organization and composition of the tegument of cestodes
12:10	Melanie Hannebelle	Swiss Tropical and Public Health Institute, Switzerland	Physics-based navigation at the air-water interface resolves the host-finding paradox in schistosome parasites
12.30	Frances Blow	University of Glasgow, UK	Single-cell RNA sequencing of Schistosoma mansoni parasites during intramammalian development

16:00 – 17:40 Session 3. exRNA interactions. Chair: Amy Buck

16:00	Collette Britton	University of Glasgow, UK	A secreted helminth microRNA suppresses gastrointestinal cell differentiation required for innate immunity
16:20	Cei Abreu-Goodger	University of Edinburgh, UK	Evolution of transposable elements as the source of extracellular RNA
16:40	Peter Nejsum	Aarhus University, Denmark	Selective packaging of anti-fibrotic and tumour suppressor miRNAs in extracellular vesicles of a parasitic whipworm
17:00	Poster Pitches 1-17 (2-minutes each)		

17:45 – 20:00 Poster Session, Posters 1-17

POSTER SESSION 1: MONDAY 8 SEPTEMBER 17:45 – 20:00

1	Manel Amri	University of Algeria	Anti-tumoral effect of *Echinococcus granulosus* hydatid fluid in a cell-derived breast cancer xenograft model
2	Geartse Bakker	Wageningen University, Netherlands	A plant-based glycobiology-oriented approach for designing vaccines against trematode infections
3	Chris Bell	University of Leeds, UK	Exosome-mediated delivery of microRNAs from plant-parasitic nematodes to plant hosts
4	Zvi Bentwich	Be-Gurion University of the Negev, Israel	Control of Schistosomiasis, Soil Transmitted Helminths and Trachoma in Africa – A comprehensive community and government intervention model
5	Bernard Marie Bitye Zambo	University of Yaounde, Cameroon	Mass drug administration of Praziquantel lowers the susceptibility of school-aged children to *Schistosoma mansoni* reinfection in endemic areas
6	Lida Derevnina	University of Cambridge	Root-Knot Nematodes unmasked: identifying and characterising their core effectorome
7	Wenda Di	Guangxi University, China	A novel *Fasciola gigantica* TGF-β ligand, FgTLP exerts unwanted proinflammatory effect in inducing macrophage polarization by binding host-derived receptor
8	Ewa Długosz	Warsaw University of Life Sciences, Poland	*Toxocara* Excretory-Secretory molecules impair the barrier function of human bronchial epithelial cells
9	Emmanuella Driciru	Leiden University, Netherlands	T cell responses in repeated controlled human schistosome infection compared to natural exposure
10	Olivia Fleming	University of Edinburgh, UK	The influence of dietary supplementation on the parasite community of wild wood mice
11	James Hewitson	University of York, UK	Generation and characterisation of a multifunctional myeloid cell reporter mouse to study type 2 immunity in helminth infection.
12	Christopher Holt	University of Baltimore, USA	Identification of sex-specific markers in *Brugia malayi* tissues
13	Rhoslyn Howroyd	University of Edinburgh, UK	Who are the superspreaders? Investigating supershedding and supercontacting in a wild rodent system
14	Elvis Leonel Kamguia Meyo	Centre for Research in Health and Major Diseases, Yaoundé, Cameroon	Reduced plasma levels of GM-CSF is a common feature of *Schistosoma mansoni*-infected school-aged children
15	Malcolm Kennedy	University of Glasgow, UK	Exquisite specificity of binding of *Trichuris* immunomodulatory proteins to extracellular matrix
16	Janina Lekki-Jóźwiak	Warsaw University of Life Sciences, Poland	The role of interleukin-6 in *Toxocara canis* infection in C57BL/6 mice
17	Paula Licona-Limón	University of Mexico	Unraveling the host-parasite interaction: regulation of the immune response in a tissue-specific manner during *N. brasiliensis* infection

Tuesday 9 September

9:00 – 10:40 Session 4. Anthelmintics & vaccines. Chair: Murray Selkirk

09:00	**Jonathan Marchant**	University of Wisconsin, USA	Exploiting the vulnerabilities of parasite TRP channels for anthelmintic development.
09:40	Petra Matouskova	Charles University, Czech Republic	How are drug-metabolizing enzymes regulated in parasitic nematodes?
10:00	Amanda Shaver	Johns Hopkins University, USA	Independent mechanisms of benzimidazole resistance across *Caenorhabditis nematodes*
10:20	Anne Lespine	INRAE, France	Genomic and transcriptomic characterization of eprinomectin resistance in *Haemonchus contortus* collected in dairy ewe farms

11:10 – 12:50 Session 5. Ecological and Evolutionary Dynamics. Chair: Amy Pedersen

11:10	Maria Yazdanbakhsh	Leiden University Medical Centre, Netherlands	Impact of maternal parasitic infections during pregnancy on immune system development at the start of life
11:30	Yoanne Mouwenda	Leiden University Medical Centre, Netherlands	Controlled human hookworm infection immune profiles in Gabon
11:50	Anne Jensen	University of Copenhagen, Denmark	The role of fermentable fibers in *Trichuris muris* infection: host susceptibility and microbial interactions
12:10	Simon Babayan	University of Glasgow, UK	Effects of dietary protein on trade-offs between growth and anti-helminth immunity
12:30	Mohammed Ahmed	University of Liverpool UK	Genomic and functional diversity of parasitism island genes in the parasitic nematode *Strongyloides ratti*

16:00 – 17:40 Session 6. Helminth-Microbe Interactions. Chair: Andy Fraser

16:00	Rory Doolan	Swiss Tropical and Public Health Institute, Switzerland	Naturalizing immunity to *Nippostrongylus brasiliensis* in the Wildling mouse model
16:20	Frédéric Fercoq	Musée National d'Histoire Naturelle, France	Stage-dependent *Wolbachia* dynamics regulate filarial development and reproduction
16:40	Mark Taylor	Liverpool School of Tropical Medicine, UK	Do viruses of filarial nematodes contribute to disease pathogenesis?
17:00	Robert Colebunders	University of Antwerp, Belgium	Virome of *Onchocerca volvulus* and its potential contribution to Onchocerciasis-Associated Epilepsy
17:20	Nolwenn Dheilly	Institut Pasteur, Paris, France	Can fluke borne viruses contribute to cancer development?

19:00 Boat Trip and Vlychos Taverna Dinner

Wednesday 10 September

09:00 – 10:40 Session 7. MINI SYMPOSIUM Chair : Lida Derevnina

09:00	**Shahid Siddique**	University of California, Davis, USA	Molecular mimicry and beyond: Roles of small secreted peptides and trans-kingdom metabolism in nematode-plant interactions
09:40	Unnati Sonawala	University of Cambridge, UK	Rooting for resistance: Characterizing the NLR immune receptor network against root-knot nematodes in sweet potato
10:00	Vincent Hanlon	University of Cambridge, UK	How and why plant-parasitic nematodes edit HYP genes in their somatic cells

11:10 – 12:50 Session 8. MINI SYMPOSIUM Chair : Unnati Sonawala

11:10	**Etienne Danchin**	INRAE, France	End of the beginning: the strange chromosome ends of root-knot nematodes
11:50	Alison Blundell	University of California-Davis, USA	Finding susceptibility in a resistance breaking world
12:10	Peter DiGennaro	University of Wisconsin, USA	Quantification of parasitic nematode feeding rates through stable isotope mass spectrometry

16:00 – 17:40 Session 9. Mucosal Interactions. Chair: Maria Yazdanbakhsh

16:00	Maria Duque Correa	University of Cambridge, UK	Unravelling interactions between populations of the intestinal stem cell niche that determine the initiation of immunity to whipworms
16:20	Hannah Peaty	Moredun Research Institute, UK	Modelling host: parasitic nematode interactions with ovine 'mini-gut' organoids.
16:40	Alasdair Nisbet	Moredun Research Institute, UK	A reverse vaccinology approach to control scour worms in sheep

17:00	Poster Pitches 18-34 (2-minutes each)

17:45 – 20:00 Poster Session 2, Posters 18-34

POSTER SESSION 2: WEDNESDAY 10 SEPTEMBER 17:45 to 20:00

18	Maria Christina Loader	City St George's, University of London	Differenctial tissue destruction and inflammatory response in soil-transmitted helminth species among TB patirnts in the Peruvian Amazon
19	Thavy Long	McGill University, Canada	Investigating the relationship between kynurenine pathway and ivermectin resistance in *Dirofilaria immitis*
20	Gloria Enjong Mbah	University of Bamenda, Cameroon	Differential susceptibility of *Onchocerca ochengi* adult male worms to flubendazole in gerbils and hamsters
21	Parul Mehra	Indian Institute of Technology Mandi, Himachal Pradesh	The *Taenia solium* novel PA1 like protein homologue modulates the mTORC1 signaling, induces anti-inflammatory response while rewiring cellular metabolism
22	Nicole Mideo	University of Toronto, Canada	Mechanistic modeling of helminth-malaria co-infections in mice
23	Jacent Nassuuna	MRC/UVRI and LSHTM Uganda Research Unit	Helminth-driven gut inflammation and microbial translocation are linked to altered vaccine responses in rural Uganda
24	Katia Oliviera	UNIFESP, Brasil	Palladacycle Compound as a Potential New Drug Against *Schistosoma mansoni*
25	Bolatito Olopade	Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria	Parasitic Pair: Uncovering the synergistic relationship between *Ancylostoma duodenale* and *Entamoeba histolytica* in a case of recurrent severe anaemia.
26	Martin Gael Oyono	Institute of Medical Research and Medicinal Plants Studies, Cameroon	The host gut microbiome alters chronic schistosomiasis-driven pathology
27	Prince Prabhu Rajaiah	Institute of Biochemistry and Molecular Biology, Hamburg, Germany	Developing a *C. elegans* system for Alzheimer's drug screening: unveiling phase separation dynamics via multiphoton imaging
28	Shafgat Shabir	Justus Liebig University Giessen, Germany	Development of an IgE-based reporter system essay for diagnosis of cystic echinococcosis in dogs
29	Ana Tahira	Instituto Butantan, Brasil	In silico and in vitro charaterization of c-jun as a downstream player of the crosstalk between S. *mansoni* and host under human TNF-alpha regulation
30	Franco Vairoletti	Institut Pasteur Montevideo, Uruguay	Novel structure-activity relationships for nematicide benzamides
31	Alexander Vidal	University of Texas Southwestern Medical Center, USA	Targeting the DAF-12 signaling pathway for the treatment of strongyloidiasis
32	Mark Viney	University of Liverpool, UK	The T-cell receptor repertoire of wild mice
33	George Wendt	University of Texas Southwestern Medical Center, USA	Evidence of ancient horizontal gene transfer in the human parasite *Schistosoma mansoni*
34	Zongsghan Zhang	Huazhong Agricultural University, Wuhan, Hubei Province, China	*In vitro* development of *Haemonchus contortus* from L3 larvae to egg-laying adults and early embryogenesis

Thursday 11 September

9:00 – 10:40 Session 10. Neurobiology & Development. Chair: Maria Duque Corrrea

09:00	**Aaron Maule**	Queen's University Belfast, Northern Ireland	Flukicide susceptibility in the liver fluke Fasciola hepatica – a question of growth?
09:40	Robin Beech	McGill University, Canada	The mechanisms generating new neurotransmitter receptors in nematodes and how to interpret diversity in multimeric proteins from an evolutionary perspective
10:00	Daniel Sprague	Medical University of South Carolina, USA	Pharmacological and computational profiling of a serotonin-responsive GPCR reveals a novel target for antiparasitic drug discovery
10:20	Albane Le Maire	Centre de Biologie Structurale, Montpellier, France	Targeting nuclear hormone receptors in parasitic nematodes for effective parasitosis treatment

11:10 – 12:50 Session 11. Co-infection and Disease. Chair: Mark Viney

11:10	Amy Pedersen	University of Edinburgh, UK	Helminth-viral coinfection interactions in a wild rodent system
11:30	Wiebke Hartmann	Bernhard Nocht Institute for Tropical Medicine, Germany	Elucidating helminth-mediated suppression of anti-influenza vaccination efficacy
11:50	Ophélie Piedfort	University of Liège, Belgium	Enteric helminth infection impairs the memory T cell response to a recombinant vesicular stomatitis virus vector vaccine
12:10	Benjamin Dewals	University of Liège, Belgium	A history of hookworm infection protects mice against a pneumovirus-induced respiratory disease via recruitment of airway $Ly6C^{+}CD64^{+}$ monocytes
12:30	Eva Pastille	University of Duisburg-Essen, Germany	Helminth-induced alterations of $CD8^{+}$ T cell immunity and its impact on colorectal cancer

16:00 – 17:40 Session 12. Immunity and Modulation. Chair: Niki Gounaris

16:00	**Christoph Klose**	Charité – Universitätsmedizin Berlin, Germany	The nervous system regulates the differentiation of epithelial cells towards the secretory lineage, promoting type 2 immunity and worm expulsion
16:40	Sara Dörken	Bernhard Nocht Institute for Tropical Medicine, Germany	Redundant and nonredundant functions of group 2 innate lymphoid cells during *Strongyloides ratti* Infection in Mice
17:00	Tiffany Bouchery	Swiss Tropical and Public Health Institute, Switzerland	NET gains: AR restores neutrophils ability to kill Schistosomes via extracellular traps
17:20	Ruby White	University of Glasgow, UK	The transforming growth factor beta mimic (TGM) family of proteins from *Heligmosomoides polygyrus bakeri* target host dendritic cells to drive regulatory immune responses.

20:30 Bratsera Farewell Dinner

Friday 12 September: Delegates depart

ALISON ELLIOTT

MRC/Uganda Virus Research Institute and LSHTM Uganda Research Unit

Alison Elliott is theme leader for Vaccine Research at the Medical Research Council (MRC)/Uganda Virus Research Institute (UVRI) and London School of Hygiene & Tropical Medicine (LSHTM) Uganda Research Unit, and Professor of Tropical Medicine at the LSHTM. She became interested in parasitology and research in Africa as an undergraduate and this interest was encouraged further by a medical student elective in The Gambia. After completing medical training she joined the London School of Hygiene & Tropical Medicine and, during the late '80s and early '90s, undertook studies on the interaction between tuberculosis and HIV infection in Zambia. An infectious diseases fellowship in Denver, Colorado, followed, providing an opportunity to learn about management of drug resistant tuberculosis and about laboratory immunology. At this time, the Th1/Th2 hypothesis had come to prominence, high-lighting the potential "antagonism" between immune responses likely to protect against tuberculosis (and to be required for effective tuberculosis vaccines) and those induced by helminths, triggering long-term interest in immunomodulation in the epidemiology of human health. Since 1997 she has been based in Uganda at the MRC/UVRI and LSHTM Uganda Unit where the Vaccine Research theme supports vaccine development for viruses, tuberculosis and schistosomiasis, and an immunomodulation and vaccines group which bridges across vaccine and non-communicable disease research. In collaboration with regional and international colleagues, this work is underpinned by research capacity strengthening in Africa.

The wonder of worms! How parasitic helminths can change our lives

Mammals, including humans, evolved in co-existence with parasitic helminth infections, and the implications of this have emerged progressively over the last half century. Infections can cause disease and disability, but are often asymptomatic, conferring subtle immunological changes that have far-reaching harms or benefits. Studies in animal models have described in compelling detail many parasite-mammal interactions, but understanding and estimating the impact of such processes on human subjects is complex due to the existence of many important co-exposures. We have used epidemiological studies, and particularly clinical trials of anthelminthic treatment in high prevalence settings, to try to determine specific effects of helminth infections on human health outcomes, and as a basis for detailed laboratory studies. With careful ethical considerations, planning and execution, such studies can allow human helminth infections to be removed, or not, for a period of time, in comparable groups of participants, based on random allocation; and outcomes of interest (such as vaccine responses, infectious disease incidence, non-communicable disease measures) can be compared with co-exposures kept "constant". Our findings indicate partially reversible effects of helminths, for example of schistosomiasis on the response to BCG vaccine, of prenatal helminth exposure on infant allergy-related disease, and of schistosomiasis on human cholesterol metabolism, and evidence that these are mediated by effects on the microbiome, metabolome and immune cell profile and function. But they also raise further questions regarding the mechanisms of observed effects, interactions between helminths and co-exposures, and the potential for immune programming which may not be altered by parasite removal. Studies in additional, contrasting populations, new approaches harnessing controlled human infection studies, and dialogue between studies in humans and animal models, have potential to address some of these further challenges with the goal of developing interventions that are beneficial for human health.

ELIA TAIT WOJNO

University of Washington, Seattle, USA

Dr. Elia Tait Wojno pursues a passion for mucosal immunology research as an Associate Professor in the University of Washington Department of Immunology. Elia received her PhD from the University of Pennsylvania, working with Dr. Christopher Hunter in the School of Veterinary Medicine. She went on to complete a postdoctoral fellowship with Dr. David Artis in the University of Pennsylvania Perelman School of Medicine and Weill Cornell Medical College, focusing on innate immune responses during helminth infection and allergic disease. At UW, she continues her work in dissecting innate and adaptive immune responses at mucosal barriers during helminth parasite infection and allergy, with a special emphasis on the role of cytokines and prostaglandins. Her work aims to inform efforts to develop new therapies and vaccines to combat parasite infection and limit allergic inflammation.

Prostaglandin regulation of Type 2 inflammation during helminth infection

The Tait Wojno laboratory investigates the cellular and molecular pathways that control type 2 immune responses during helminth infection and allergic disease. Helminth infection and allergy are associated with a polarized type 2 inflammatory response. In helminth infection, this response is host-protective, while during allergy, this response causes pathology and is a result of inappropriate reaction against harmless allergens. Type 2 inflammation is characterized by activation of innate and adaptive immune cells such as group 2 innate lymphoid cells, basophils, and $CD4^+$ T helper type 2 (Th2) cells; production of the cytokines interleukin (IL)-4, IL-5, IL-9, and IL-13; and activation of epithelial cells that results in goblet cell hyperplasia and enhanced mucus production. While previous work has highlighted many pathways that regulate adaptive Th2 responses, our understanding of innate immune and epithelial cell responses during type 2 inflammation remains incomplete. Studies in the Tait Wojno laboratory take a unique approach to address this gap in knowledge. Ongoing studies focus on unraveling how bioactive lipids called prostaglandins and their receptors intersect with cytokine pathways to promote and resolve type 2 inflammation. Employing murine models of parasite infection and allergy alongside analysis of human samples allows us to dissect how cytokines, lipids, and cell-cell interactions shape type 2 inflammatory responses at mucosal tissues during helminth infection and allergy.

JONATHAN MARCHANT

The Medical College of Wisconsin, USA

Jonathan is a Professor & the Marcus Chair of Cell Biology, Neurobiology & Anatomy at the Medical College of Wisconsin. He received a PhD in Pharmacology at the University of Cambridge working on ion channel kinetics, before studying spatial and temporal compartmentalization of local signaling events in cells supported by a Wellcome Trust postdoctoral Fellowship at the University of California, Irvine. He started at lab at the University of Minnesota before moving to MCW in 2017. The Marchant laboratory tries to understand the molecular choreography of calcium signaling events in cells and how things go awry in various disease states. None of this sounds anything remotely to do with parasitology, were it not for our persistent curiosity to explain a phenotype discovered in our lab, where the anthelmintic drug praziquantel screws up regeneration of planarian flatworms to cause bipolar worms. This challenged us to figure out how praziquantel worked, leading to our recent discovery of a specific parasitic flatworm ion channel ($TRPM_{PZQ}$) that is the target of this essential therapy. Having insight into how this old but essential drug works provides new opportunity for drug design for various parasitic flatworm infections, and will spur better understanding of the fascinating role of TRP channels in parasite biology.

Exploiting the vulnerabilities of parasite TRP channels for anthelmintic development.

The broad portfolio of ion channels expressed by parasitic flatworms presents promising opportunities for drug development. A great example is provided by transient receptor potential ion channel superfamily (TRP channels), which are well established in mammalian systems as critical transducers of various environmental cues into changed cellular responses. Throughout the schistosome life cycle, multiple transitions through differential physiochemical niches must occur, making TRP channels intriguing suspects for helping parasites sense and adapt to their local environments. If so, then these channels may be especially vulnerable to anthelmintic attack, and in this regard our work has shown that two members of a specific TRP channel subfamily (TRP melastatin, or TRPM channels) are selectively activated by the clinical drug praziquantel ($TRPM_{PZQ}$), and the anthelmintic benzodiazepine meclonazepam ($TRPM_{MCLZ}$). These dual TRPM channels and their siblings represent great targets for anthelmintic design, and this presentation will discuss our latest progress in understanding these targets and a healthy dose of speculation as to their unique vulnerabilities and how we can exploit them to combat various diseases caused by parasitic flatworms.

SHAHID SIDDIQUE

University of California Davis, USA

Shahid Siddique is an Associate Professor in the Department of Entomology and Nematology at the University of California, Davis. He earned his Ph.D. from BOKU—University of Natural Resources and Life Sciences, Vienna, Austria—then spent several years at the University of Bonn, Germany, as a post-doctoral researcher and later a research-group leader. Since joining UC Davis in 2019, he has built a research program that couples fundamental discovery with biotechnological solutions for agriculture. His lab uses plant-parasitic nematodes and their hosts as model systems to investigate the evolution and molecular basis of host–parasite interactions. A central goal is to understand how nematodes meet their nutritional and metabolic needs inside plants—insights that reveal vulnerabilities to exploit for crop protection. Beyond basic research, the lab applies advanced genomics, CRISPR editing, and host-induced RNA interference to translate discoveries into practical nematode-control strategies. These efforts are pursued in close collaboration with grower organizations and other stakeholders to ensure solutions are both scientifically sound and tailored to agricultural needs.

Molecular mimicry and beyond: Roles of small secreted peptides and trans-kingdom metabolism in nematode-plant interactions

Plant-parasitic nematodes are highly evolved obligate parasites that threaten global food security. These parasites have a remarkable ability to establish elaborate feeding sites in roots, which are their only source of nutrients throughout their life cycle. A wide range of nematode secretions has been implicated in modulating host pathways to suppress defenses and promote feeding-site formation. To develop more effective and sustainable interventions, we need a deeper understanding of how these parasites satisfy their nutritional and metabolic requirements within the host. In my talk, I will present two complementary themes that shed light on these host–parasite exchanges. First, I will describe how nematodes deploy secreted small peptides—exemplified by PSY-like sulfated peptides (MigPSYs) from root-knot species—that closely mimic plant peptide hormones to manipulate host development and facilitate parasitism. Second, I will discuss trans-kingdom metabolic exchanges that meet nematode dietary demands, focusing on vitamin metabolism, using pantothenate (vitamin B5) as a key example. Together, these examples illustrate how molecular mimicry and trans-kingdom metabolism operate in concert to support nematode parasitism and highlight metabolic vulnerabilities that could be exploited in future control strategies.

ETIENNE DANCHIN

Institut Sophia Agrobiotech, INRAE, Sophia Antipolis, France

Etienne G.J. Danchin is an INRAE senior scientist and leader of the research team 'Genomics & Adaptive Molecular Evolution'. He is also the scientific lead of the bioinformatics and genomics platform of Institut Sophia Agrobiotech. He is mainly interested in understanding relationships between genomic variations and adaptive evolution. At ancient timescales, he studies the inter-species genomic signatures and singularities associated with evolution of parasitism. For instance, he has documented the importance of horizontal gene transfers in the evolution of a plant-parasitic lifestyle. At more contemporary scales he studies intra-species genomic variations associated with adaptation to environmental changes and to control methods against pests and parasites.

Etienne's main study model since he was recruited as an INRAE scientist in 2007 are the root-knot nematodes, a group of devastating agricultural pests. In 2014, he obtained an accreditation diploma from the University Côte d'Azur, Nice, France in the field of adaptive genome evolution, to supervise PhD students and lead research projects. Previously, as a postdoc, at the CNRS (Marseille, France) from 2004 to 2007 he has annotated and compared repertoires of carbohydrate-active enzymes (CAZymes) in fungal genomes. This allowed identifying some idiosyncratic CAZyme repertoires specific to fungal phytopathogens. During his early career as a PhD student at Aix-Marseille University (2001-2004; he has mainly studied evolutionarily conserved synteny in animal genomes and gene losses in vertebrates.

End of the beginning: the strange chromosome ends of root-knot nematodes

Chromosome ends are protected by nucleoprotein complexes called telomeres. Shortening of telomeres following DNA replication as cell divide is responsible for ageing; while their dysfunction is involved in several cancers. Telomeres are usually composed of G-rich repetitive DNA associated with a complex of proteins and RNA. Together, they stabilize chromosome ends and prevent them from being fused or recognized as DNA breaks. Telomeres shortening is partially compensated by telomerase reverse transcriptase that multiply the DNA repeat using RNA templates. This canonical system is thought to be widely conserved across evolution. This includes the model nematode *C. elegans* whose telomeric repeats TTAGGC are multiplied by telomerase enzymes, with a whole set of single-strand and double-strand telomeric DNA-binding proteins identified and characterized. Recent advances in long-read genome sequencing technologies have yielded genome assemblies at near-chromosome scale for a variety of nematode species. This allowed exploring how conserved / different telomeric systems are in the nematode tree of life. We found a lot of variations in nematode telomeric systems. For instance, simple short repeats and telomerase were missing in many animal and plant-parasitic nematodes. We focused our analyzes on root-knot nematodes, one of the most damaging agricultural pests. We found that these species featured a diversity of complex repeats at the ends of their chromosomes. Different telomeric repeats seem to have been recruited in each clade of root-knot nematodes and they all lack homology in the rest of species. Furthermore, telomerase and orthologs of the *C. elegans* shelterin complex were missing, suggesting an alternative lengthening of telomeres. This discovery opens new perspectives, including possible control methods specifically targeting telomeres.

AARON MAULE

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Aaron Maule completed his PhD in Experimental Parasitology in 1989, subsequently working as a postdoctoral researcher in both Biology and Medicine at Queen's before moving to the United States to work in the pharrmaceutical industry (The Upjohn Company / Pharmacia, Kalamazoo, MI, USA; 1992-95). He subsequently returned to Queen's as a lecturer, obtaining a Chair in Molecular Parasitology in 2001. Over the last 20 years he has severed as Research Director, Head of School, Faculty Dean of Research and Interim Pro Vice Chancellor for Medicine, Health and Life Sciences before recently returing to his first academic home in Biological Sciences to focus on the biology of parasitic worms!

With his research team work has previously centred on improving the understanding of nervious system structure and function in selected flatworm and roundworm parasites, with a particualr focus on neuropeptides, building phenotypic and functional genomics toolsets to aid experimental enquiry. Over the last decade or so his research team's effors have narrowed to focus on the liver fluke, Fasciola hepatica, with the devleopment of a molecular toolbox that faciliates both short term and long-term in vitro studies of juvenile fluke biology, adding the ability to monitor and manipulate growth which is strating to shed light on novel aspects of liver fluke biology.

Flukicide susceptibility in the liver fluke *Fasciola hepatica* – a question of growth?

As the causative agent of fasciolosis, Fasciola spp. impose a major disease burden on ruminant livestock and cause a neglected tropical zoonosis. Migratory liver stage juveniles cause acute disease that can result in death, whilst the bile duct stage adults cause chronic disease. Most flukicides target the adult with one flukicide, triclabendazole (TCBZ), effective against both juveniles and adults. TCBZ resistance is common and new control options need to effectively control the juvenile worm to counter acute disease. In vitro drug-responses in TCBZ-susceptible and TCBZ-resistant field isolates revealed that in vivo resistance in juveniles did not correlate well with motility responses to TCBZ, but did correlate with growth and cell proliferation phenotypes. Liver fluke juveniles grow quickly during their liver migration, a process supported by the proliferation of stem-cell like neoblasts. In vitro manipulation of worm growth using irradiation or RNAi revealed that reducing the growth rate in resistant fluke increased drug susceptibility and enhancing growth in susceptible fluke reduced drug susceptibility, allowing us to switch phenotypic responses between resistant and susceptible fluke, simply by manipulating growth. The data support the hypothesis that growth dynamics can play a key role in drug susceptibility, and potentially resistance. Indeed, examination of the in vitro growth of an array of resistant and susceptible fluke field isolates, exposed a strong correlation between growth and drug susceptibility. Further, the interrogation of selected stem cell targets in fluke using gene-silencing exposed growth dysregulation as a common phenotypic readout, but also exposed some lethal phenotypic outcomes, including the over proliferation of fluke stem cells and mitotic catastrophe in association with the dysregulation of key effectors in cell development and apoptosis. The data encourage the consideration of growth dynamics as a factor in anthelmintic susceptibility and further support the repurposing of cancer-stem cell targeting drugs for parasite control.

CHRISTOPH KLOSE

Department of Microbiology, Infectious Diseases, and Immunology of Charité Universitätsmedizin Berlin

Christoph Klose earned his Ph.D. in Molecular Medicine from Albert-Ludwigs-University in Freiburg in 2007. Following his doctoral studies, he conducted post-doctoral research at Weill Cornell Medicine in New York City before establishing an independent Emmy-Noether research group at the Department of Microbiology, Infectious Diseases, and Immunology of Charité - Universitätsmedizin Berlin. Dr. Klose's research has significantly contributed to our understanding of immune cell lineage commitment and development, with a particular focus on innate lymphoid cells (ILCs). In recognition of his contributions, he was awarded the Robert Koch post-doctoral Immunology award in 2015 and has been listed as a Highly Cited Researcher by Clarivate Analytics since 2020. The main focus areas of his research group are (1) The interaction between the immune system and the nervous system, particularly at barrier surfaces, and (2) the role of ILC2s in type 2 immunity.

The nervous system regulates the differentiation of epithelial cells towards the secretory lineage, promoting type 2 immunity and worm expulsion

Intestinal epithelial homeostasis is sustained by the continuous differentiation of stem cells that are located at the bottom of the intestinal crypts. Epithelial renewal is a highly dynamic process that receives signaling input from various cellular systems to secure barrier function and nutrient uptake. Here, we addressed the enteric nervous system's (ENS) role in this process. We identify a pivotal function of the ENS in controlling epithelial proliferation, differentiation, and mucosal homeostasis. Neuronal VIP acting via its receptor VIPR1 on epithelial stem cells restrains proliferation and differentiation towards the secretory lineage. Deficiency of VIP or VIPR1 led to an increase in secretory epithelial cells, including tuft cells, increased IL-25 expression, and activation of ILC2. Functionally, VIP deficiency improved worm expulsion and exacerbated allergic lung inflammation. Our data expose a previously unappreciated role of the ENS in dictating epithelial cell fate decisions, thereby establishing a neuro-epithelial unit as a critical checkpoint for type 2 immunity.

1 Exploring helminth-derived TGF-β mimics as modulators of inflammatory disease

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Helminth parasites have evolved sophisticated methods to avoid clearance by the host immune system and promote their long-term survival. The murine nematode *Heligmosomoides polygyrus* produces a range of secreted products with immunomodulatory functions, many of which promote immune regulation. Among these proteins, a family of 10 novel TGF-β mimics (TGMs) has been identified. The first, TGM1, mimics the ability of mammalian TGF-β to drive differentiation of regulatory T cells *in vitro*, while administration *in vivo* ameliorates airway inflammation and colitis. In addition to binding host TGF-β receptors, TGMs bind cell-specific co-receptors such as CD44, which confer cell selectivity in their activity that the mammalian cytokine cannot achieve. Beyond this, the mechanisms through which TGM1 drives protective responses *in vivo* remain incompletely understood, and the outcome of TGM signalling for different cell populations *in vivo* remains largely unknown. To determine how the TGM family modulates host immune responses *in vivo*, we first administered fluorescently labelled TGMs, and confirmed that different family members show preferential binding to distinct cell types *in vivo*. The dissemination of fluorescent TGMs can be tracked to different tissues, allowing interrogation of binding to different tissue-resident populations. Using transgenic mice lacking previously identified coreceptors, we can now determine the requirement for these coreceptors across diverse cell types. Finally, we aim to determine the functional effects of TGM binding for different populations, and are exploring how different members of the TGM family alter the outcome of inflammatory disease in the context of colitis.

2 The cellular targets and parasite immunomodulation of IL-33 signalling in *Heligmosomoides polygyrus bakeri* infection

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IL-33 is an alarmin cytokine that binds its receptor ST2 to initiate a type 2 immune response. IL-33/ST2 signalling is important for worm ejection – ST2 knockout mice are more susceptible to infections with the intestinal nematode *Heligmosomoides polygyrus bakeri* (*Hpb*), while *Hpb* secretes a range of proteins to inhibit this pathway and enhance its survival in the host. To investigate the cellular response that is important in IL-33-dependent anti-*Hpb* responses, we have generated a range of conditional ST2 knockout mice. In infection experiments, mast cell-conditional ST2 knockout ($MCPT5^{Cre}IL1RL1^{flox/flox}$) mice showed increased faecal egg burden and worm fecundity, with unchanged Th2 responses and mast cell degranulation. Bulk RNA-seq of intestinal tissue showed reduced expression of neutrophil-associated genes in $MCPT5^{Cre}IL1RL1^{flox/flox}$ mice, thereby suggesting a role for IL-33 signalling in a mast cell-neutrophil axis that may be important in anti-helminth immune responses. This reduced expression of neutrophil-associated genes was seen in naïve $MCPT5^{Cre}IL1RL1^{flox/flox}$ mice as well. As such, tonic mast cell IL-33 signalling may be important in producing an anticipatory neutrophil response to reduce parasite fecundity. The importance of IL-33/ST2 signalling in the anti-helminth immune response is further highlighted by the fact that *Hpb* secretes HpARI (which blocks IL-33) and HpBARI (which blocks ST2, the IL-33 receptor). Vaccination of mice with HpARI and HpBARI proteins led to the generation of blocking antibodies which could release the host from *Hpb*-mediated immunosuppression, leading to increased type 2 immune responses, and robust immunity to the parasite. Together, this work highlights that the IL-33 pathway is critical for ejection of parasitic worms, and provides proof-of-concept that parasite-derived immunomodulators can be used as effective vaccine antigens.

3 Modulation of host epithelia by excretory-secretory products from ovine gastrointestinal parasitic nematodes

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The mechanistic analysis of host:parasite interactions for many gastrointestinal nematodes is hampered by lack of accessibility to the site of infection. To model these interactions, we have recently developed organoid cultures from ovine tissues to model the interaction of *Teladorsagia circumcincta* (a gastric dwelling parasite) and *Trichostrongylus colubriformis* (an intestinal dwelling parasite). Using organoids matched to the site of parasite infection we have demonstrated that excretory-secretory (ES) products produced by infective stages of these parasites can modulate host physiological and immune responses. Interestingly, we demonstrate that early parasitic stages of *T. circumcincta*, but not *T. colubriformis*, produce excretory-secretory (ES) protein/s that are able to rapidly expand gastric organoids by inducing fluid secretion into the lumen of the organoid. We suggest that this mechanism is required by *T. circumcincta* to invade and expand gastric glands of the stomach. Current work is underway to identify *T. circumcincta* ES molecule/s driving organoid expansion and to understand their mechanism of action. The availability of chromosome-level genomes for both species, along with stage-specific transcriptomes and proteomes will expedite this process. The identification of these molecule/s and the mechanism of how parasites modulate host immunity and physiology may offer a new route to discovering novel actives for treating or preventing gastrointestinal nematode parasites of livestock.

4 A new way to see metabolism — smol-seq brings the power of DNA sequencing to metabolomics

June H. Tan and **Andrew G. Fraser**

The Donnelly Centre, University of Toronto

Over the last 40 years there has been a revolution in the power of DNA sequencing. It is millions of times faster and this has made nucleic acids easy to analyse from genomes to RNAseq to single-cell analyses. The explosion of DNA sequencing power has also been harnessed in experimental assays from drug screens to protein-protein interaction mapping that use DNA sequencing as an output. If an assay can be configured to have a DNA sequence output, this dramatically increases both depth and speed since it allows the massively parallel multiplexing of assays. I'm going to present a new method for reading metabolite or drug levels with DNA sequencing — this harnesses the power and ease of DNA sequencing for metabolomics. We call this smolSeq for '**Small MOLecule quantification by sequencing**'.

The entire approaches relies on aptamers as sensors. Aptamers are short oligonucleotides that have high affinity and specificity for a target. Structure-switching aptamers are a specific class of aptamer sensors — these undergo a very large conformational change on binding their target. That conformational change allows them to be used as sensors. In this talk I'll describe the entire smol-seq system, the specificity and sensitivity of the sensors and where the technology sits right now. We hope that having a simple sequencing-based metabolomics platform will allow researchers to probe the complex effects of parasite infection on both host and parasite metabolism. What I'd love is to interact with other attendees and see if they have specific targets that they would like us to develop sensors for — this could lead to new analysis tools and diagnostics reagents.

5 Structural and functional insights into the nuclear receptor DAF-12 from different parasitic nematodes

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Nuclear receptors are ligand-gated transcription factors that regulate essential biological processes, including metabolism, development, and reproduction. Due to their lipophilic ligands and ability to modulate multiple genes within the same pathway, they have emerged as attractive targets for the development of therapeutic molecules. Notably, nuclear receptors are present across all categories of helminths, where they contribute not only to development and reproduction but also to survival by enabling adaptation of the worm to various environmental stresses. Among them, DAF-12 is one of the most studied receptors. However, its mechanism of action and regulation in parasitic nematodes remains poorly understood, with limited data available on transcriptional coregulators in these organisms. To address this gap, we recently solved the crystal structure of DAF-12 from two parasitic nematodes, *Brugia malayi* and *Haemonchus contortus*, in complex with mammalian coactivator peptides. Structural analysis, combined with mutagenesis experiments, provided new insights into the receptor's mechanism of action. Based on these structural data and on a comparative genomic analysis of parasitic nematodes, we are searching for novel coactivators in these organisms. Our findings advance the understanding of nuclear receptor function in helminths and may inform future strategies for targeting parasitic nematodes with small-molecule therapeutics.

6 Cellular organization and composition of the tegument of cestodes

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Parasitic flatworms are covered by a highly modified syncytial epidermis known as the tegument. In cestodes, the tegument is the only site of interaction between the parasite and the host, however the details of its organization and physiology are essentially unknown. Benzimidazoles such as albendazole are the only chemotherapeutic drugs available for treatment of *Echinococcus* spp. infections in humans. Although their molecular target is beta-tubulin, it is not clear which cell types are affected by these drugs, although classic experiments have shown damage to the tegument at high drug concentrations. Using the model cestode *Mesocestoides corti*, we described the organization of the cytoskeleton of the tegument, finding an abundance of microtubules in an apico-basal orientation, suggesting a role in intracellular traffic. We then analyzed the effects of therapeutically relevant concentrations of albendazole, finding that it specifically resulted in the disappearance of microtubules in the tegument, but not in other tissues. Metabolic labeling of newly synthesized proteins demonstrated that albendazole reduced the incorporation of new proteins in the distal tegument and produced an unexpected overall decrease in protein synthesis. On a complementary approach, we characterized the composition of the tegument of the cestodes *M. corti*, *Hymenolepis microstoma* and *Echinococcus multilocularis* by proteomic analysis on tegument-enriched fractions, identifying hundreds of tegument-enriched proteins, validating a subset by immunofluorescence and *in situ* hybridization. By comparative bioinformatic analysis, we obtained a core set of tegument-enriched proteins conserved in parasitic flatworms, and to functionally study some of the identified proteins, we developed a tissue specific *knock-down* method based on morpholino oligomers, with very promising results showing the alteration of the splicing of target genes. This work represents an important advance in our understanding of the tegument and its sensitivity to albendazole, and incorporates valuable new tools for the study of these parasites.

7 Physics-based navigation at the air-water interface resolves the host-finding paradox in schistosome parasites

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Schistosome parasites affect over 200 million people worldwide despite a fundamental ecological paradox: their free-swimming larvae (cercariae) are short-lived, sparsely distributed, and cannot overcome natural water flows that surpass their swimming speeds—conditions that should severely limit their ability to find human hosts. Here we resolve this paradox by demonstrating that cercariae use a previously unknown physics-based strategy: they actively accumulate and swim along the air–water interface, where ambient flow velocities are significantly reduced. High-resolution imaging revealed that 86% of cercariae preferentially localize at the water surface, transforming an inefficient threedimensional search into an effective two-dimensional exploration, thereby increasing host-encounter efficiency by three orders of magnitude. Biomechanical modeling shows this behavior emerges naturally from a weight-asymmetric morphology, enabling four distinct swimming modes without the need for sophisticated neural control. Our results identify the air–water interface as a critical, yet unrecognized microhabitat for parasite transmission, and suggest new physical interventions targeting this interface to mitigate schistosomiasis transmission.

1

8 Single-cell RNA sequencing of *Schistosoma mansoni* parasites during intramammalian development

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The parasitic flatworm *Schistosoma mansoni* has a complex lifecycle, including multiple body plan transitions, two hosts and two free-living stages. During intramammalian development, juvenile parasites migrate through the portal system, from the liver to blood vessels of the intestine, where they undergo extensive morphological changes resulting in sexual maturation, pairing, and reproduction. Deconvoluting developmental processes underlying these changes will identify parasite vulnerabilities that can be exploited for the control of schistosomiasis. Single-cell RNA sequencing atlases have provided snapshots of gene expression patterns from around the *S. mansoni* lifecycle, including larvae, juveniles and adult parasites. However, linking these discrete snapshots together to determine trajectories of cellular development between stages remains a key challenge. We, therefore, performed single-cell RNA sequencing of parasites collected from multiple timepoints in experimentally infected mice, to capture heterogeneous mixtures of juvenile parasites enriched for earlier and later development. The combined dataset covers a continuum of development from which we are using RNA velocity to place cells of several tissues, including muscle and neurons, into developmental trajectories. By analysing expression at positions along these trajectories, genes that potentially drive differentiation can be found. Using RNA interference to manipulate expression, we will determine the roles of these genes in parasite development. Once this temporal cell atlas is completed, identifying key steps in parasite development and transmission, novel targets for control strategies against schistosomiasis will be revealed.

9 A secreted helminth microRNA suppresses gastrointestinal cell differentiation required for innate immunity

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Helminths are masters of immunomodulation, secreting products that suppress host immune responses, leading to chronic infection and making vaccine development challenging. While helminth excretory-secretory (ES) products involved in immunoregulation have been identified, little is known of the mechanisms by which they suppress host responses. We previously identified small regulatory microRNAs in ES products of the important veterinary nematode *Haemonchus contortus*. Several of these were conserved in nematodes infecting the gastrointestinal (GI) tract, but not in tissue-dwelling filarial nematodes. This led us to speculate that these GI nematode miRNAs may play important roles in regulating host genes and modulating the gut environment. Consistent with this, miR-5352 was detected in abomasal tissue and draining lymph nodes of *H. contortus*-infected animals, indicating release *in vivo* and potential to modulate host gene expression. To examine effects of nematode miRNAs on host GI tissue, we combined the use of GI organoids, bioinformatic target prediction and gene expression analysis. We focussed on mir-5352, a nematode-specific miRNA conserved across diverse GI nematodes including hookworms and *Ascaris*. Transfection of murine or ovine GI organoids with a mimic of mir-5352 suppressed cytokine-mediated differentiation of organoid secretory cells, including tuft and mucous cells, and promoted stem cell maintenance. Mechanistically, this was achieved through targeted repression of critical host factors, including transcription factor Klf-4 and the IL-22 receptor, leading to modulation of Wnt and Notch signalling pathways. Nematode miR-5352 shows seed sequence conservation with mammalian miR-92a family members, indicating that through convergent evolution, GI nematodes exploit a host miRNA regulatory network to suppress host innate responses, promote tissue regeneration and establish a favourable environment for chronic infection.

10 Evolution of transposable elements as the source of extracellular RNA

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Beyond self-replicating, transposable elements (TEs) can be a source for new functions. Small RNAs (sRNAs) and Argonaute proteins are important for silencing TEs, however, sRNAs can also be effector molecules for some parasites. The parasitic nematode *Heligmosomoides bakeri* can modulate the immune response of mice by secreting a variety of molecules including proteins, lipids, sRNAs and the extracellular worm Argonaute (exWAGO). Importantly, secreted sRNAs are mostly derived from TEs, suggesting a relationship between TE silencing and parasitism. *H. bakeri* has one of the largest, TE-rich, nematode genomes. Nevertheless, little is known about the evolution of these TEs, or their functions in parasitism. Using immunoprecipitation (IP) of exWAGO in *H. bakeri*, and sequencing bound sRNAs, we found that they map to all major classes of TEs, with a preference for particular families. LTR/Pao and LTR/Gypsy retrotransposons seem particularly relevant, producing ~8-fold more sRNAs than expected. IP experiments in *H. polygyrus*, *Nippostrongylus brasiliensis*, *Teladorsagia circumcincta,* and *Ancylostoma ceylanicum* confirm that, although their genomes vary in size and TE composition, exWAGO preferentially loads sRNAs derived from LTRs. We also found that not all LTRs are relevant for secreted exWAGO in *H. bakeri* and observe that certain properties of LTRs are associated with sRNAs present inside extracellular vesicles. We propose exWAGO as an ancestral regulator of retrotransposon activity. Parasitic nematodes have since gained the capacity to secrete exWAGO and sRNAs during infection, alongside an expanded and diverged repertoire of transposable elements in their genomes.

11 Selective packaging of anti-fibrotic and tumour suppressor miRNAs in extracellular vesicles of a parasitic whipworm

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Parasitic helminths still infect over 1.5 billion people worldwide despite the availability of effective anthelmintics. Infections are often chronic and sterilizing immunity is lacking, due in part to effective host-immune manipulation by helminths. Extracellular vesicles (EVs), nanosized membranous particles with bioactive cargoes of lipids, proteins and nucleic acids are implicated in intercellular communication within organisms. Indeed, it is now clear that EVs released from parasites are capable of inter organismal communication with their host. Here we have extensively characterized the physical properties, protein and nucleic acid cargoes of EVs released by *Trichuris suis* as a well-established porcine model of human *T. trichiura* infection. Surprisingly, *T. suis* EVs did not mediate immune modulatory effects whereas, non-vesicular secretory products potently downregulated inflammatory cytokine production by immune cells. By generating the first extracellular miRNA complement for *T. suis* and assessing miRNA expression we identified selective EV packaging of miRNAs. Of note, two miRNAs enriched in EVs from adult worms were orthologues of the human anti-fibrotic and tumour suppressor miRNAs, *hsa-miR-22-3p* and *hsa-miR-29b-3p.* Indeed, *tsu-miR-29-3p* downregulated collagen type I expression in an in vitro fibrosis assay. Finally, using a proteomics approach in human colon cancer cells we demonstrate that *tsu-miR-22-3p* and *tsu-miR-29-3p* are functional and downregulate experimentally validated targets of these human tumour suppressor miRNAs.

In summary, identification of functional orthologues of anti-fibrotic and tumour suppressor miRNAs in *T. suis* EVs suggests that whipworm EVs may function outside the host-immune modulatory paradigm and could present a novel extension to the hygiene hypothesis.

1 Anti-tumoral effect of *Echinococcus granulosus* hydatid fluid in a cell-derived breast cancer xenograft model

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Breast cancer remains the most frequently diagnosed cancer in women worldwide, with conventional treatments often limited by serious side effects and therapeutic resistance. In recent years, the ability of various helminths and derived products to suppress cancer growth has been well documented, both in humans and in experimental models. We aimed to investigate the potential antitumor effects of *Echinococcus granulosus* hydatid fluid (HF), known for its immunomodulatory properties, in a cell-derived breast cancer xenograft (CDX) model. For this purpose, immunosuppression was first induced in Wistar rats using cyclosporine A (CsA). Subsequently, HF treatment was followed by xenograft of human HEP2 tumor cells. Key parameters monitored throughout the experimental protocol included the rats' overall health statuts, body weight, circulating immune cell populations, nitric oxide (NO) and interleukin-6 (IL-6) production. HF treatment resulted in notable changes in the overall health and immune responses of the rats. Treated rats showed improved weight regain, increased monocytes and neutrophils counts, and increased NO/IL-6 production, indicating enhanced immune response activation. Remarkably, only 20% of HF-treated rats developed tumors, compared to 80% in untreated rats, with a significant reduction in tumor size. Additionally, HF-treated rats exhibited lower levels of hepatic transaminase, indicating reduced toxicity. These finding suggest that hydatid fluid not only enhances the immune response but also effectively inhibits tumor growth with minimal toxicity. This study highlights the potential of hydatid fluid as a promising therapeutic approach for breast cancer. Further research is recommended to understand the molecular mechanisms underlaying the effects of HF. This new antitumor strategy could open new perspectives in the development of highly immunogenic anticancer vaccines.

2 A plant-based glycobiology-oriented approach for designing vaccines against trematode infections

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Trematode infections, such as *Schistosoma mansoni* and *Fasciola hepatica*, have a major impact on human and animal health worldwide. Treatment of these infections currently relies on the use of anthelminthic drugs, but are not always efficient as reinfections often occur and threats of drug resistance are increasing. Vaccines could provide a more sustainable control strategy against these trematodes, but to date no commercial anti-trematode vaccines are available. The development of vaccines against parasitic worms is challenging in terms of antigen selection as well as production of recombinant subunit vaccines. Several studies have shown the protective capacity of native antigens isolated from the parasite, but recombinant variants of the same antigens often fail to give the same level of protection. In our lab we have previously delivered proof-of-concept that the protective capacity of a recombinant vaccine against a nematode parasite requires the reconstitution of the native N-glycan composition of the vaccine candidate. In the current study we exploited our plant-based expression system to produce recombinant glycoproteins from trematode parasites, engineered with native glycan elements found in these parasites. We selected Cathepsin B1 from *S. mansoni* and Cathepsin L3 from *F. hepatica* as vaccine targets. These cathepsins are proteases implicated in host invasion, feeding and immunomodulation that were associated with some level of protection in previous vaccination studies. Both vaccine candidates were successfully produced and purified in our plant-based system, and we were able to engineer a diverse set of native glycan elements, ranging from high-and low mannose structures to more complex N-glycan motifs. In the future, this highly versatile platform will reveal whether N-glycan engineering can be used to increase the protective capacity of cathepsin-based vaccines, and will allow further investigation into the role of N-glycans in shaping anti-parasite immunity.

3 Exosome-mediated delivery of microRNAs from plant-parasitic nematodes to plant hosts

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MicroRNAs are ~22-nucleotide-long noncoding RNAs that regulate gene expression through post-transcriptional gene silencing. Typically, this results in the negative regulation of target genes. Plant-to-pathogen and pathogen-to-plant cross-kingdom RNAi via microRNAs occurs in both defence and virulence mechanisms, respectively. Multiple plant microRNAs are known to regulate plant defence and the formation of feeding structures induced by root-knot nematodes. However, the presence of plant-parasitic nematode microRNAs, their mode-of-delivery into host tissues, and their potential role in nematode virulence is unknown. Here, transmission electron microscopy confirmed the presence of exosome vesicles in resorcinol-induced secretions of *Meloidogyne incognita* second-stage juveniles. Small RNA Sequencing of this exosome fraction identified multiple microRNAs including one of particular interest that is predicted to target host plant systemic acquired resistance via auxin responsive pathways. *In situ* hybridisation chain reaction of this nematode microRNA indicated expression in the subventral glands, confirming the potential for secretion into the plant and highlighting a potential role in root invasion and early parasitism. Exogenous application of the nematode microRNA to roots, with predicted uptake and systemic translocation via the xylem, increased infection by root-knot nematodes. Current research is now aiming to determine the role of nematode exosomes in host-nematode interactions and the repertoire of microRNAs that they may contain.

4 Schistosomiasis Transmission in Relation to Seasonal and Spatial Dynamics of Freshwater Snail Populations in Ethiopia

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Background: Understanding the dynamics of freshwater snail populations and their role in schistosomiasis transmission is critical for optimizing control strategies in endemic regions. Schistosomiasis, caused by parasitic flatworms of the genus *Schistosoma*, remains a major public health burden in tropical and subtropical regions. The parasites undergo part of their life cycle within freshwater snails, releasing infectious cercariae into the water, which can penetrate human skin and lead to infection.
Methods: This study investigates the seasonal and spatial variations in snail abundance and infection patterns in Mizan Aman, Southwest Ethiopia, to support targeted interventions. Data were collected from 20 freshwater sites across three distinct seasons: one dry and two wet seasons. Key environmental parameters, including temperature, pH, and salinity, were analyzed to understand their influence on snail populations and infection rates.
Results: A total of 1,616 snails, predominantly *Biomphalaria pfeifferi* and *Biomphalaria sudanica*, were collected and examined. Significant seasonal fluctuations were observed, with snail abundance peaking during the dry season, likely due to stable habitat conditions, such as reduced water turbulence and water levels. Environmental factors influencing the snail populations were salinity during the dry season and total dissolved solids and conductivity during the wet period. Snails' infection rate was examined by cercaria shedding assays. In some collection sites like Agu, high infection rates were consistently recorded across all seasons. Clear correlation was observed between seasonal variations in snails infection rates and parasite shedding and epidemiological data on human infection rates.
Discussion: The results of this stucy highlight the important role snails infection rates and parasite shedding play in the spread of Schistosomal infection among humans living in these environments. Monitoring and controling snail populations should play a major role in all Schistosoma elimination programs. This study underscores the need for seasonally adaptive and site-specific control strategies for effective schistosomiasis management and transmission prevention.

5 Mass drug administration of Praziquantel lowers the susceptibility of school-aged children to *Schistosoma mansoni* reinfection in endemic areas

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This study examines how regular praziquantel treatment influences schistosomiasis transmission dynamics and its associated health effects, including anemia, tissue fibrosis, and cognitive impairment, in school-aged children. Previously collected samples and associated data from SAC with various cumulative numbers of annual rounds of PZQ received were analyzed in relation to infection rates, parasite burden, morbidity by quantifying plasma levels of IgE, IgG4, type-2 cytokines and metabolites. The data showed that regular administration of PZQ to SAC associated with a significant decrease in their odds (AOR = 0.16, 95% CI = 0.01-0.61) to harbor elevated parasite burden when re-infected. These SAC regularly receiving annual PZQ presented with better hemoglobin levels (AOR = 2.58, 95% CI = 1.22-8.05) and had better academic results (AOR = 2.39, 95% CI = 1.11-7.09). Regular PZQ treatment was associated with higher protective IgE levels (p = 0.002) and IgE/IgG4 ratios (p = 0.03) with higher type-2 plasma cytokine production (IL-4: p = 0.04, IL-33: p = 0.03). Additionally, metabolomics profiling revealed a heightened activation of the Arginine/Proline metabolism (i.e. higher hydroxyproline, p = 0.01; higher L-proline, p = 0.01 and higher L-Glutamate 5-semialdehyde, p = 0.03) in this population group. However, regular administration of PZQ did not reduce the likelihood to develop liver fibrosis upon infection (AOR = 1,73, 95% CI = 0.45-14.53). Our work therefore proposes a hitherto poorly described advantage of sustained administration of PZQ to SAC from schistosomiasis-endemic area whereby regular deworming with PZQ might protect against heavy reinfection and its sequelae.

6 Root-Knot Nematodes unmasked: identifying and characterising their core effectorome

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Root-knot nematodes (RKNs, *Meloidogyne* spp.) cause substantial agricultural losses, surpassing billions of dollars annually. To successfully parasitize their hosts, RKNs produce and secrete effectors to suppress the plant immune system and reprogram host physiology. The majority of effectors are synthesized in the nematode's oesophageal gland cells and injected into plant cells via a syringe-like stylet. Despite their central role in pathogenicity, only a few RKN effectors have been functionally characterized. Comparative transcriptomics of infected roots identified 3- and 5-days post-inoculation as key early parasitic stages, marked by transcriptional shifts and effector gene enrichment indicative of stage-specific regulation. Analysis of predicted secreted proteins across multiple RKN species has also revealed conserved orthogroups that likely underpin RKN parasitism. To enable refined effector discovery, gland cell isolation techniques for RKNs have been optimised to facilitate targeted transcriptomics of the effector-producing cells themselves. Sequencing of the gland cells at key parasitic stages will allow us to define the effector repertoire in RKNs with unprecedented spatial and temporal precision. Together, these approaches lay the foundation for defining an RKN effectorome, identifying conserved parasitism genes and dissecting the molecular mechanisms underpinning nematode infection.

7 A novel *Fasciola gigantica* TGF-β ligand, FgTLP exerts unwanted proinflammatory effect in inducing macrophage polarization by binding host-derived receptor

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Tissue arrested L3 (TaL3) larvae pose a significant challenge to hookworm control due to their resistance to drugs. A deeper understanding of TaL3 development process is critical for effective ancylostomiasis management. However, current knowledge on TaL3 development remains limited. In this study, infective L3 (iL3) of *Ancylostoma ceylanicum* were subcutaneously injected into 6-week-old female KM mice (500 larvae per mouse), and TaL3 were collected from muscle tissues 16 days post-infection. The average length of TaL3 is 681.7 ± 28.4 μm, which is significant longer than that of iL3(624.1 ± 22.2 μm) ($P < 0.01$). The average width of TaL3 is 27.8 ± 3.0 μm, while width of iL3 is 24.1 ± 2.5 μm. Beisides, TaL3 exhibited distinct cavities, excretory orifices, and more fully developed intestinal tubes and esophageal bulbs than that of iL3. *In vivo* deworm by ivermectin showed that high-dose ivermectin (1 mg/kg) couldn't dewormed TaL3 completely, with a reduction rate of 81.7%. Furthermore, an in vitro culture system was established, achieving 90% feeding rate for TaL3, which could be applied for TaL3 development exploration. High-concentration RNA inhibitors inhibited TaL3 feeding, suggesting RNA synthesis is essential for TaL3 development. Finaly, the transcriptomic profiling of TaL3 were seqenced, showing divergent transcriptional abundance to that of iL3. 50 highest-transcribed genes in TaL3 were screened, among of which, 16 genes were ribosomal-associated proteins, indicating protein synthesis is essential for TaL3 development. Besides, ubiquitin B, superoxide dismutase, and heat shock protein also diaplayed highest transcription, and functional validation of these genes (e.g., via inhibitor assays) will performed to assess their roles in TaL3 development.

8 *Toxocara* Excretory-Secretory molecules impair the barrier function of human bronchial epithelial cells

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Experimental studies have demonstrated that infection with *Toxocara canis* results in chronic pulmonary inflammation and induces a dominant Th2-type immune response. Furthermore, *T. canis* infection leads to tracheal inflammation, thickening of the tracheal smooth muscle layers, and narrowing of the trachea, eventually leading to the development of asthma-like symptoms. Interestingly, not only type 2 cytokines have been detected in hosts infected with *T. canis*, but an upregulation of IL-6 has also been noted in serum, bronchoalveolar lavage fluid, and ex vivo splenocyte cultures. The correlation between IL-6 and asthma, as well as other pulmonary diseases, is well established. IL-6 is a pleiotropic cytokine released by various cells and is believed to have different functions depending on its context. Classic IL-6 signaling mediates the activation of anti-inflammatory pathways in target cells, while trans-signaling (IL-6TS) activates the immune system by recruiting monocytes to inflamed areas. Additionally, IL-6TS inhibits regulatory T lymphocyte differentiation and promotes the differentiation of Th17 cells. Studies show that a subset of asthmatic patients - referred to as the IL-6TS-high subset - exhibits activation of the lung epithelial IL-6TS pathway. This activation leads to increased airway inflammation, disruption of epithelial barrier function, submucosal inflammation, and tissue remodeling. We analyzed the effect of *T. canis* larval antigens on the epithelial barrier using 16HBE14o- human bronchial epithelial cell line depending on simultaneous IL-6 trans-signaling. Changes in barrier permeability were noted using transendothelial electrical resistance measurements, and tight junction proteins – occludin and ZO-1 - were analyzed using western blotting and immunostaining. Our study provides new data on *T. canis* interaction with respiratory tissues, giving new insights into the pulmonary immune reaction to lung-dwelling helminths. A better understanding of these aspects of the infection will hopefully help to improve the therapeutic methods of human toxocariasis.

9 T cell responses in repeated controlled human schistosome infection compared to natural exposure

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Despite repeated praziquantel treatment mainly through mass drug administration in schistosomiasis-endemic settings, the lack of sterilizing immunity against this parasitic disease results in continuous re-infection. Insights into immune kinetics during reinfection have remained a daunting challenge, mainly due to difficulty in tracking natural infection in the human host. We utilized a novel repeated (3x) controlled human *Schistosoma mansoni* infection model (repeated-CHI; Netherlands, n= 24) to investigate how T cell responses develop during reinfection. Further, we compared our findings to natural infection in a schistosomiasis-endemic setting (Uganda, n= 13). *Schistosoma*-specific $CD4^+$ T-cell and cytokine responses were assessed using spectral flow cytometry and Luminex. In repeated-CHI, a mixed array of Th1/Th2/regulatory T cell response develops, primarily against adult-worm-antigens. This response is markedly increased during sequential exposure to cercariae of different sexes (male-female-male) compared to single-sex (male-male-male) exposure. Male-female-male exposure additionally promoted an elevated cytokine response to adult-worm- and egg-antigens. Naturally-infected endemic participants showed differential cytokine response to egg- and cercariae-antigens. However, adult worm-specific cytokine response in natural infection was similar to single-sex repeated-CHI. Overall, our findings highlight translatability of the CHI model to natural infection in endemic settings and advance our understanding of the immunology of *Schistosoma*-(re)infection.

10 The influence of dietary supplementation on the parasite community of wild wood mice.

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Humans have dramatic impacts on the resources available to wildlife; decreasing the availability of shelter, food, and water through urbanisation, agricultural intensification and over-harvesting. However, the provisioning of food to wildlife, both accidentally (for example, household waste) and intentionally (for example, bird feeders), is also widespread. We have previously found evidence that additional food can reduce the burden of helminth parasites in wood mice (*Apodemus sylvaticus*), a prevalent rodent which naturally inhabits UK forests, as well as improving the efficacy of anthelmintic treatments. We hypothesised that the effects of food supplementation on disease would be dependent on the quality and distribution of the food, as costly immune responses may be permitted by the availability of micro- and macro-nutrients, and behavioural modifications to access food resources may modify the rate of parasite transmission between individuals. Here, we use experimental supplementation of the food available in a wild environment, to investigate how food quality and distribution affect helminth infection intensity and prevalence, as well as the gastrointestinal parasite and ectoparasite communities of wood mice. We demonstrate that social contacts and movement are affected by the availability of aggregated versus evenly distributed food. This work has interesting implications for how modified food availability due to anthropogenic change may influence disease transmission in wild animals.

11 Generation and characterisation of a multifunctional myeloid cell reporter mouse to study type 2 immunity in helminth infection.

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Myeloid immune cells adopt divergent activation states following infection with intracellular bacteria/protozoa (type 1 immunity) *vs*. extracellular parasitic helminths (type 2 immunity). Existing transgenic mouse models to study myeloid cell function generally report or manipulate only a single cell type, and rarely assess *in vivo* cell activation. To address this deficit, we are creating a multicolour myeloid cell transgenic reporter/deletor/fate-mapping mouse ("MyeT mouse") that allows simultaneous detection and manipulation of macrophages, neutrophils and eosinophils, as well as reporting their classical (iNOS) and alternative (RELMα) activation status. Macrophages, neutrophils and eosinophils are each labelled with *Csf1r*-BFP, *Mmp9*-human CD2 or *Epx*-human CD4. These constructs also drive the expression of split recombinases fused to chemical-inducible dimerisation domains (i.e. N-Cre-ABI and N-FlpO-GID1). Myeloid cell activation is marked by *Nos2*-tdTomato and *Retnla*-citrine, and these constructs also encode the C-terminus of the split recombinases and dimerisation domains (PYL-C-Cre and GAI-C-FlpO, respectively). Treatment with the phytohormones abscisic acid (Cre) or gibberellin (FlpO) induces recombinase activation and excision of STOP sites to allow fate mapping (Rosa26-reporter) or cell deletion (Rosa26-DTX). In addition, Ms4a3-Dre recombinase x Rox-STOP-Rox-Katushka labels monocyte-derived cells and distinguishes these from macrophages of embryonic origin. Our initial experiments revealed reduced M-CSF receptor expression from transgenic alleles leading to embryonic lethality in homozygous mice, whereas BFP(+) monocytes and macrophages are readily detected in heterozygotes. We treated *Retnla*-citrine mice with IL-33 or schistosome eggs and found RELMα/citrine reporter expression in both macrophages and eosinophils, as well as a population of peritoneal macrophages that constitutively expresses RELMα in naive animals. We are currently characterising the other transgenic lines, which will also include *Nippostrongylus brasiliensis* and *Schistosoma mansoni* infections. This mouse resource is available to the wider research community through the UKRI National Mouse Genetics Network.

12 Identification of sex-specific markers in *Brugia malayi* tissues

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Brugia malayi, a human infective filarial nematode, is used in the laboratory to study lymphatic filariasis. We sought to examine tissue-specific gene expression and chromatin state profiles using single nuclei methods and the 10X Genomics multiome method. We isolated 200,000 nuclei that were on average 7 um from 20 gravid adult *B. malayi* female worms. Approximately 10,000 nuclei were used to successfully generate snRNAseq and snATACseq libraries that were sequenced on an Illumina NovaSeq generating ~20,000 snRNAseq reads and ~25,000 snATACseq reads per nuclei. Reads were attributed to single nuclei and counted in Cell Ranger with subsequent clustering using Seurat, Signac, and other related tools in R. WNN multiome dimensional reduction and clustering using both data sets resolved the nuclei into clusters associated with tissues including muscles and the hypodermis. A major portion of nuclei are attributed to embryos, and a significant amount of snATACseq data is from the *Wolbachia* endosymbiont, as expected. Pseudobulk expression analysis shows tissue-specific and stage-specific gene expression. Male and female embryos could only be resolved through dimensional reduction that integrated both the gene expression and ATAC-seq data. Once resolved, nuclei from male and female embryos were sexed using gene expression and chromatin markers on the X and Y chromosomes and had similar but not identical expression profiles. Many of the markers for the clusters formed from the WNN dimensional reduction were proteins of unknown function. In cases where the cluster function is known, we can begin the process of attributing preliminary functions to these genes of unknown function. However, there are entire clusters that lacked any marker with a known function, highlighting how little we know about these important medical parasites.

13 Who are the superspreaders? Investigating supershedding and supercontacting in a wild rodent system

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Parasitic helminths play vital roles in natural ecosystems where they can drive host dynamics and structure ecological communities. They are also a major health and economic concern worldwide. A ubiquitous feature of helminth infection is the over dispersed (aggregated) distribution, where the majority of infection (~80%) is found within a minority of hosts (20%). These highly infected individuals may act as 'superspreaders', driving transmission by releasing large numbers of infective stage parasites into the environment. Superspreaders can be further divided into two key groups: 'supercontactors' and 'supershedders', allowing the distinct evaluation of social contact and parasite shedding rates on shaping parasite transmission. However, the identity of supercontacters and supershedders is often unknown in a population, and attempting to identify such individuals on a short-term timescale would be unfeasible for any disease control policies. Therefore, using a wild rodent system, I will investigate which factors correlate with an individual being classed as a supercontactor or a supershedder. Specifically, I will be using the wild rodent *Apodemus sylvaticus* and one of its natural parasites, *Heligmosomoides polygyrus*. I will determine whether factors including host sex, age, body condition, and coinfection with external and internal parasites correlate with an individual's identity as a supercontactor and/or supershedder. My results demonstrate how various morphometric, demographic and co-infection factors can help to identify hosts contributing disproportionately to parasite transmission in natural systems, allowing targeted treatment to aid parasite transmission prevention.

14 Reduced plasma levels of GM-CSF is a common feature of *Schistosoma mansoni*-infected school-aged children

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Schistosomiasis is a neglected tropical disease (NTD) that persists despite global control efforts. Diagnosis in low burden settings and logistically easy to use morbidity monitoring tools are needed to eliminate the disease as a public health problem. Since, the infection associates with a dynamic host cytokine response, Through the comparison of parasite burden and host factors, we assessed whether host plasma cytokines could be used as robust biomarkers for intestinal schistosomiasis and associated pathology in school-aged children(SAC) living in endemic areas. Levels of host plasma cytokines were measured in SAC from a low-to-moderate burden region five months deworming with praziquantel, using Luminex assay for exploration analysis and ELISA for validation. From a preliminary screening of 27 plasma cytokines by Luminex on discovery cohort, only GM-CSF, IL-2 and VEGF were altered by the host infectious or pathology profile. Cytokine-specific ELISA assays on validation cohort confirmed children with *S. mansoni* infection to present with significant lower plasma levels of GM-CSF and IL-2 when compared to *S. mansoni*-negative children. Further assessment of the biomarking potential of these cytokines revealed a negative correlation between plasma levels of GM CSF, but not those of IL-2, and *S. mansoni* egg burdens in infected individuals. Moreover, when applying a threshold of plasma GMCSF levels for the screening of *S. mansoni* at-risk children, we could achieve an augmentation of the sensitivity of a single Kato-katz by at least 20%. Finally, a ROC Curve of GM-CSF performance yielded an AUC of 75%, confirming the possible use of plasmatic levels of GM-CSF as good predictive marker of *S. mansoni* infection in our study. In conclusion, our work revealed the potential of biomarking *S. mansoni* infection by comparative measurements of plasma GM-CSF. A basis for the refined use of plasma GM-CSF as a Schistosomiasis adjunct diagnostic tool is herein suggested.

15 Exquisite specificity of binding of *Trichuris* immunomodulatory proteins to extracellular matrix

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Whipworms *(Trichuris sp.)* are prevalent soil transmitted helminths of both humans and animals. Infections are chronic and acquired immunity is slow to develop and partial. We use the mouse model of whipworm (*T. muris*) to define the mechanisms of resistance and susceptibility to infection. We have recently shown that the major secreted molecule from *T. muris* (p43), a dorylipophorin, Tm-DLP-1, binds signalling-associated lipids, extending its known binding to extracellular matrix glycosaminoglycans, especially heparan sulphate (HS) and the cytokine interleukin (IL-)13. We here confirm remarkable similarities between the p43 orthologue from human whipworm, *T. trichiura,* p47, Tt-DLP-1 and present new data on the unusual high binding specificity of both p43 and p47 to HS.

We previously showed that addition of IL-13 to HS/p43 complexes causes p43 release from HS allowing IL-13 to subsequently interact, a mechanism now also confirmed for p47. Preincubation of p43 with IL-13 prevents efficient p43/HS interaction, suggesting overlapping/interacting binding sites, a finding further supported by molecular dynamic simulations (MDS). We hypothesise that during chronic infection p43/p47 released by the worm tethers to the increased extracellular matrix (ECM) (HS) expressed by the infected epithelium and surrounding niche. When IL-13 is present it competitively replaces binding of p43/47 to HS and prevents IL-13 activity. Using a CHOcell glycoarray (GAGOme), we now show exquisite specificity of the binding of p43/47 to HS through a single rare type of 3-O-sulphation catalysed by a single enzyme, 3-O-sulfotransferase 2 (HS3ST2). *Hs3st2* expression is markedly elevated during chronic *T. muris* infection. Finally, HS binding to p43 is dependent on zinc and also for p47. Thus, zinc binding/co-ordination could play a determining role in regulating initial p43 binding to HS and subsequent release from p43 for IL-13 binding. Our p43 MDS suggests a potential zinc coordination site between Glu360 and Glu379. Taken together, our data suggest whipworms have evolved a multifunctional immunomodulatory molecule derived from a major internal lipid transporter with binding specificities tailored to controlling its intestinal niche during chronic infection.

16 The role of interleukin-6 in *Toxocara canis* infection in C57BL/6 mice

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Toxocariasis is a common zoonotic disease with a global seroprevalence of 19%, classified as a neglected disease by the Centers for Disease Control and Prevention. Infection occurs through the ingestion of eggs from *Toxocara* species, primarily *T. canis* or *T. cati*. In paratenic hosts, such as rodents and humans, larvae hatch in the intestines and migrate throughout the body, causing organ damage and leading to symptoms like fever, myalgia, weight loss, cough, rashes, and hepatosplenomegaly. Our recent studies with splenocyte cultures from *T. canis*-infected mice revealed increased interleukin 5 (IL-5) and elevated IL-6 levels, suggesting that IL-6 may play an important role in the infection's pathogenesis. Due to its pleiotropic nature, IL-6 can exert both pro-inflammatory and anti-inflammatory effects, making its role in toxocariasis unclear. What is more, studies using IL-6 knockout mice in helminth infection models suggest a multifaceted impact on immune responses. This study aims to describe the impact of IL-6 deficiency on *T. canis* infection in mice, focusing on local immune responses in the lungs. Female C57BL/6 IL-6 knockout and wild-type mice were infected with *T. canis* invasive eggs and euthanized at various time points. Cytokine expression in the lungs was measured by ELISA, and fibrosis-related gene expression was analyzed by qPCR. Additionally, the number of larvae was quantified at different infection stages. IL-6 knockout mice showed changes in larval counts and distribution. Moreover, the levels of antibodies and cytokines differed between experimental groups. We expect this study to improve our understanding of the immunological mechanisms regulating toxocariasis and determine whether IL-6 could be a potential therapeutic target, similar to its role in rheumatoid arthritis.

17 Unraveling the host-parasite interaction: regulation of the immune response in a tissue-specific manner during *N. brasiliensis* infection

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Hookworm infection is a disease of global relevance caused by helminthic parasites that reside in the intestines of various organisms, including humans, primarily affecting children in developing countries. These parasites adapt to their hosts by modulating immune responses or using the host to their advantage. Host-parasite interaction occurs mainly through excretory-secretory products (ESPs), which differ between species and stages of worm development. In the laboratory, we use *Nippostrongylus brasiliensis* as a hookworm model to identify, through transcriptomic analysis, genes specifically induced in the host by the parasite in a tissue-specific manner, as well as ESP products derived from the parasite at different developmental stages (L3, L4, and L5). With this approach, we plan to identify specific ESPs that could modulate the host immune response in a time- and organ-specific manner and to unravel new interactions to better understand the complex biology of interspecies communication. We identified proteins from the SCP-TAPS (sperm-coating protein, Tpx-1/Ag5/PR-1/Sc7) family that were expressed in a stage-specific manner and were also ESPs. Interestingly, this family of proteins has been associated with the regulation of the immune response. We selected a candidate molecule induced in the skin of infected mice, an ESP from the L3 stage. Our candidate, called Nb-SCP-2, is similar in amino acid sequence and structure to Na-ASP-2, an ESP derived from *Necator americanus*, a hookworm that affects humans and has been associated with the regulation of leukocyte migration. We cloned and recombinantly expressed our protein in insect cells. We purified the protein and demonstrated, using the air-pouch inflammation model, that this recombinant protein is capable of recruiting neutrophils, a population important for controlling sheath-exsheath and migration of the larvae throughout the host. We are currently characterizing the potential use of this protein to promote or modulate the immune response during the infection *in vivo*.

1 How are drug-metabolizing enzymes regulated in parasitic nematodes?

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Drug resistance is a major obstacle to effective pharmacotherapy for many diseases, including helminthiases. The parasitic helminth *Haemonchus contortus* has developed resistance to all major classes of anthelmintics. In resistant helminth strains and those exposed to sub-lethal doses of anthelmintics, increased drug deactivation and efflux—mediated by the upregulation of drug-metabolizing enzymes (DMEs)—have been observed. However, the mechanisms by which nematodes adapt to anthelmintics, as well as the regulatory pathways controlling DME expression, remain largely unknown. Understanding these resistance-related regulatory processes in *H. contortus* could provide valuable insights into its defense mechanisms. Several genes involved in albendazole detoxification, including *P-glycoprotein 9.1* and *UDP-glucosyl transferase 365A1*, are known to be upregulated upon albendazole exposure. However, the molecular players driving this upregulation remain unidentified. Gene regulation of DMEs can occur at multiple levels, and we hypothesize that transcriptional regulation is mediated by specific nuclear hormone receptors (NHRs) or transcription factors (TFs). Although limited, existing evidence supports this hypothesis—*NHR-176* has been shown to mediate the response to thiabendazole, while *NHR-8* is involved in ivermectin response in *Caenorhabditis elegans*. Recently, the *H. contortus* NHR family was thoroughly characterized, providing a foundation for further investigation. In our study, transcriptomic analysis of *H. contortus* exposed to low-dose albendazole revealed several deregulated genes, including one transcription factor and one nuclear hormone receptor. Our ongoing research focuses on confirming the direct binding of albendazole to these candidate regulators using isothermal titration calorimetry. Additionally, we are developing loss-of-function *C. elegans* mutants to validate their role in the xenobiotic response. We propose that the identified NHR and TF play a crucial role in mediating the xenobiotic response in *H. contortus*. These factors may serve as promising targets for novel compounds with antagonist activity, potentially enhancing anthelmintic efficacy and delaying resistance development.

2 Independent mechanisms of benzimidazole resistance across *Caenorhabditis* nematodes

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Benzimidazoles (BZs), a widely used class of anthelmintic drugs, target beta-tubulin proteins, disrupt microtubule formation, and cause nematode death. In parasitic nematode species, mutations in beta-tubulin genes (*e.g.*, *isotype-1 beta-tubulin*) are predicted to inhibit BZ binding and are associated with BZ resistance. Similarly, in the free-living nematode *Caenorhabditis elegans*, mutations in an *isotype-1 beta-tubulin* ortholog, *ben-1*, are the primary drivers of BZ resistance. The recurrent association of BZ resistance with mutations in beta-tubulin genes is an example of repeated evolution of drug resistance across diverse nematode species. To evaluate this hypothesis, we identified predicted BZ resistance alleles in beta-tubulin genes across wild strains from three *Caenorhabditis* species: *C. elegans*, *C. briggsae*, and *C. tropicalis*. We hypothesized that if these species experienced similar selective pressures, they would evolve resistance to BZs by mutations in any of three beta-tubulin genes (*ben-1*, *tbb-1*, and *tbb-2*), which are expressed in multiple tissues and implicated in tubulin polymerization dynamics. Using high-throughput assays, we tested the association of natural beta-tubulin alleles with BZ resistance. We found that a heterogeneous set of variants identified in *Cel-ben-1* were associated with BZ resistance. In *C. briggsae*, only two variants unique to *Cbr-ben-1* (W21stop and Q134H) were associated with BZ resistance. In *C. tropicalis*, two unique missense variants were identified in *ben-1*, but neither was associated with BZ resistance. Because no variants in *ben-1* were associated with BZ resistance in *C. briggsae* and *C. tropicalis*, we tested whether predicted mutations in *tbb-1* and *tbb-2* were associated with BZ resistance. We found that variants in *tbb-1* or *tbb-2* in *C. briggsae* and *C. tropicalis* were not associated with BZ resistance. Our findings reveal a lack of repeated evolution of BZ resistance across the three *Caenorhabditis* species and highlight the importance of defining BZ resistance mechanisms outside the beta-tubulin gene family.

3 Genomic and transcriptomic characterization of eprinomectin resistance in *Haemonchus contortus* collected in dairy ewe farms

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Anthelmintic resistance significantly impacts both animal welfare and productivity. At the heart of this issue is *Haemonchus contortus*, a highly pathogenic gastrointestinal nematode of small ruminants. In this study, we examined eprinomectin (EPR) resistance in *H. contortus* using a unique set of samples collected from French dairy sheep farms in a small geographic area of southwest France, where EPR is routinely used as a deworming treatment, with several cases showing alarming clinical failures.
Six worm isolates characterized for their susceptibility or resistance to macrocyclic lactones (ML) using a motility assay on 3 stage larvae were used in this study (see abstract A. Lespine). DNA was extracted from L3 for advanced genome-wide approaches based on sequence comparisons. In addition, adult males and females were recovered from infested animals in order to conduct a transcriptomic study.
The dataset provides a unique opportunity to link significant genomic and gene expression variations with worm phenotypic data and farm treatment histories. In EPR-resistant worms, a discrete genomic region on chromosome V exhibited significant genetic differentiation, which had previously been identified as a signature of ivermectin resistance in *H. contortus*. Moreover, we observed variations in the expression of genes located on chromosome V that could be associated with the resistance phenotype.
This paves the way for identifying novel molecular targets, forming the basis for improved diagnostics and treatments for helminth infections.

4 Impact of maternal parasitic infections during pregnancy on immune system development at the start of life

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The variation in the human immune system and the contribution of non-heritable factors to the diversity in immunological profiles has gained much interest, but there are very few studies focusing on early life. Using mass cytometry, we compared the immune cell profiles of neonates in Africa and Europe, and went on to examine the impact of maternal malaria and helminth infections during pregnancy. Significant immunological differences were seen between European and Gabonese, particularly in hematopoietic stem and progenitor cells (HSPCs), in addition to both myeloid and lymphoid compartment. Further analysis revealed differences that were linked to maternal parasitic infections. Examining the trajectory of HSPCs revealed that Europeans and placental malaria-exposed Gabonese shared a similar differentiation pattern with elevated myeloid progenitors and reduced NK/ILC progenitors, supported by higher frequencies of cytotoxic $CD16^{+}$ NK cells and non-classical monocytes, compared to Gabonese without placental malaria. Moreover, maternal helminth infection was associated with increased ILC-2, $CD16^{-}$ NK cells, and myeloid dendritic cells. An increased TNF-producing NK cells in Europeans and placental malaria-exposed Africans as well as IL-4, -5, and -13-secreting ILCs in helminth-exposed Gabonese neonates indicated that parasitic infections modulate the cellular function. Taken together, these findings underscore that maternal parasitic infections are one of the non-heritable factors, that during pregnancy can impact the *in utero* development of the immune system.

5 Controlled human hookworm infection immune profiles in Gabon

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Hookworm infections affect over 200 million people worldwide, with high reinfection rates limiting the effectiveness of mass drug administration. Despite the global burden, the immune mechanisms regulating host-parasite interactions remain poorly understood. To address this, controlled human hookworm infection (CHHI) models have been established primarily in developed countries, limiting insight into how lifelong hookworm exposure shapes the immune system. To bridge this gap, we established the first controlled human hookworm infection (CHHI) model in Gabon, an endemic region for *Necator americanus*. In this study, 16 healthy Gabonese participants were experimentally infected with 50 *N. americanus* larvae, with immune and clinical assessments performed at multiple time points (D0, Wk4, Wk8, Wk12, Wk16). Peripheral blood mononuclear cells (PBMCs) were collected for high-dimensional immune profiling, including single-cell CyTOF analyses, to track immune changes over time. Our aim is to determine how controlled infection in an endemic population compares to CHHI in non-endemic individuals. Early results suggest that plasmacytoid dendritic cells (pDCs) and regulatory T cells (Tregs) undergo dynamic remodelling in Europeans who underwent CHHI, resembling immune profiles observed in Indonesians with natural hookworm infections. However, Tregs were not as suppressive derived from lower expression of key markers associated with immunoregulatory activity. By directly comparing immune responses between endemic and non-endemic CHHI cohorts, we seek to understand how chronic helminth exposure and environmental factors influence immune tolerance and resistance mechanisms. This study provides a unique opportunity to explore helminth-induced immunomodulation in different geographic contexts, with direct implications for vaccine development and therapeutic strategies against *N. americanus*.

Keywords: *Necator americanus*, Controlled Human Infection, Immune Modulation, Single-Cell Immunophenotyping, Vaccine Development

6 The role of fermentable fibers in *Trichuris muris* infection: host susceptibility and microbial interactions

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Parasitic worms infect over a billion people globally, contributing to malnutrition and morbidity. These infections interact with the host immune system and gut microbiota (GM), with the worm's own microbiome potentially playing a role. **However, the precise interactions between the intestinal worms and the bacteria in the host gut have not been elucidated.** Inulin, a fermentable fiber, is metabolized by the GM and can alter microbial composition and activity. Given these effects, we investigated how dietary fermentable fibers and antibiotic treatment influence host susceptibility to *Trichuris muris* infection and the role of the worm microbiome. Mice were fed diets containing fermentable fibers (chow or inulin) or a non-fermentable fiber diet (cellulose) for 14 days prior to infection. Inulin- and chow-fed mice exhibited significantly higher worm burdens than cellulose-fed mice, suggesting that fermentable fibers enhance host susceptibility. Host microbiome analysis revealed substantial differences between inulin- and chow-fed mice, yet the worm microbiomes remained stable across dietary groups. To assess the role of the host microbiome in infection, antibiotic treatment was administered. While antibiotics significantly reduced host GM alpha diversity, they had little impact on the worm microbiome alpha diversity and did not alter worm infectivity. Worm microbiomes were consistent between antibiotic-treated and untreated mice, demonstrating their stability even under conditions of host-microbial perturbation. These findings demonstrate that dietary fermentable fibers increase susceptibility to *T. muris* infection, though apparently not via host GM alterations. Furthermore, the stability of the worm microbiome, even under antibiotic-induced perturbation, underscores its resilience within the host environment.

7 Effects of dietary protein on trade-offs between growth and anti-helminth immunity

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Life history theory predicts fundamental trade-offs between growth and immunity under resource constraints, yet the causal mechanisms remain unresolved. Using Structural Causal Modelling and semi-parametric Targeted Maximum Likelihood Estimation (TMLE), we analysed mice from lines selected for high (ROH) or low (ROL) growth potential under primary and secondary *Heligmosomoides bakeri* infections and high vs. low protein diets. TMLE with Super Learners revealed that ROH mice had higher levels of type 1 immune markers, including iNOS expression in the gut (β = 0.304, 95% CI: [0.000, 0.608]) and IgG2a in serum (β = 0.713, 95% CI: [0.394, 1.032]), as well as increased IL-17 in serum (β = 0.901, 95% CI: [0.424, 1.378]) relative to ROL mice. In contrast, they showed lower levels of type 2 immune markers, including IL-10 production stimulated by antigen in vitro (β = −0.985, 95% CI: [-1.490, -0.480]) and IgE in serum (β = −0.169, 95% CI: [-0.286, -0.051]). High-protein diets (230g/kg) enhanced type 2 immunity, with increased IL-4 in serum (β = 0.240, 95% CI: [0.093, 0.388]) while suppressing IFN-γ production (β = −0.743, 95% CI: [-0.498, -0.989]). Structural causal modelling identified a significant three-way interaction between host genotype, dietary protein level, and parasitic infection treatment: in ROH mice, a high-protein diet significantly reduced gut iNOS expression following infection and subsequent ivermectin treatment (β = −2.367, 95% CI: [−4.362, −0.372]), implying that low-protein diets (30g/kg) may exacerbate Th1 responses in ROH mice after recovering from infection, potentially contributing to an increased inflammatory state and impaired resolution of immune responses. These results suggest that protein scarcity forces prioritisation of skeletal growth over type-2 parasite defence, with nutritional interventions rescuing immunity without compromising genetic potential. Our semi-parametric approach provides mechanistic insights into resource allocation trade-offs, indicating potential targets for sustainable livestock breeding and nutritional strategies against human helminthiasis.

8 Genomic and functional diversity of parasitism island genes in the parasitic nematode *Strongyloides ratti*

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Strongyloides ratti is a common parasitic nematode of rats. It has *c.* 900 genes associated with parasitism. Among these are genes encoding astacin-like metalloproteases, acetylcholinesterases (AChEs), CAP-domain containing proteins, and Transthyretin-like proteins. Many of these genes are arranged adjacently in gene clusters referred to as “parasitism islands”. In UK *S. ratti* populations these parasitism islands have higher levels of polymorphisms than other genomic regions. Most of these polymorphisms are non-synonymous, suggesting functional divergence among gene products of the island genes. To explore the functional impact of such variation in the island genes, we have analysed genomes and characterised the parasitism islands from several wild UK *S. ratti* genotypes by long-read DNA sequencing. We find that parasitism island structure is diverse among different genotypes, both in the number of islands in each genome (ranging from 38 to 50), their genomic position, and their gene composition. Focusing on astacin-like metalloproteases, structural protein modelling and alignment with experimentally-determined structures shows that over 85% of parasitism island encoded astacins lack the zinc-binding motif that is essential for protease activity. This loss contrasts with astacins encoded outside of parasitism islands, where most retain the motif and, presumably, protease activity. Because genes encoding these motif-deficient astacins are highly expressed we suspect that they may have alternative, non-protease functions such as substrate binding. Similarly, most of the AChE-coding genes result in proteins that are missing key motifs and residues required for catalytic activity. Phylogenetic analysis of these proteins suggests that, unlike the astacin-like metalloproteases, non-canonical AChEs coding genes did not all evolve exclusively in *Strongyloides*. However, like the astacin-like metalloproteases their expansion did coincide with the evolution of parasitism in *Strongyloides*.

9 Naturalizing immunity to *Nippostrongylus brasiliensis* in the Wildling mouse model

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Hookworm infection afflicts around 500 million people worldwide and additional tools are needed to achieve the WHO NTD roadmap, including the development of a vaccine to reduce morbidity. Current laboratory models of human infection fail to replicate a key characteristic of human hookworm infections, namely that no protective immunity is established. The 'translational hurdle' of generating clinically relevant insights from laboratory mouse models is widely observed in biomedical research and 'naturalization' has been proposed as a solution. Naturalized mice are exposed to microbes, pathogens or even the natural environment to better induce immune system maturation. Here we implement the Wildling mouse model to study helminth infection and immunity in mice with a complex microbiome and exposome. While SPF laboratory mice display near full protection towards *Nippostrongylus brasiliensis* reinfection, we observed that Wildlings are susceptible to reinfection, in line with human observations. This is associated with a dampening of type 2 immunity in the T cell and ILC2 compartments throughout infection, as observed by scRNAseq and flow cytometry. During primary infection, morphological characteristics of *N. brasiliensis* from Wildling mice and SPF mice were similar. Interestingly, we observed a delay in expulsion of the parasite. In the small intestine, we found that the prototypical anti-helminth 'weep and sweep' response was delayed in Wildling mice, with both tuft cell numbers and goblet cell hyperplasia reduced as compared to SPF mice. Naturalizing helminth research could thus bridge the current translational gap and offer a unique understanding of the host-helminth interaction.

10 Stage-dependent *Wolbachia* dynamics regulate filarial development and reproduction

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Filarial nematodes, responsible for diseases such as lymphatic filariasis and onchocerciasis, rely on *Wolbachia* endosymbionts for development and reproduction. Understanding the factors regulating parasitic nematode development is key to deciphering the mechanisms underlying parasite fitness and transmission. While parasitic helminths rely on host cues for development, filarial nematodes additionally depend on *Wolbachia* endosymbionts for survival and reproduction. *Wolbachia* have therefore emerged as key therapeutic targets, but their stage-specific role and interactions with host immunity remain poorly understood. Using the rodent filaria *Litomosoides sigmodontis*, we investigated the impact of *Wolbachia* depletion on larval development and the influence of type-2 immune responses on bacterial distribution and density in adult filariae. Experimental infections in wild-type and *Il4rα*$^{-/-}$*Il5*$^{-/-}$ type-2-immunity-deficient mice, combined with qPCR, fluorescence *in situ* hybridization, and confocal microscopy, revealed that *Wolbachia*-free microfilariae developed into infective L3 larvae within the vector but failed to mature beyond L4 in vertebrate hosts, exhibiting early growth retardation after the L3-to-L4 moult, with progressive defects in body elongation and reproductive organ differentiation leading to developmental arrest. In adult filariae harbouring *Wolbachia*, the host driven type-2 immune environment selectively reduced *Wolbachia* densities in the female germline, coinciding with impaired oogenesis, embryogenesis, and microfilarial output, while somatic *Wolbachia* remained unaffected. These findings raise the possibility that host immunity may not act directly on *Wolbachia* but could instead influence bacterial dynamics indirectly through metabolic or endocrine alterations affecting germline homeostasis. To conclude, our study demonstrates stage-specific *Wolbachia* dependency, with distinct contributions to larval development and adult reproduction. These findings enhance our understanding of host-parasite-endosymbiont interactions and inform the refinement of antifilarial strategies targeting *Wolbachia*.

11 Do viruses of filarial nematodes contribute to disease pathogenesis?

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Recently we have discovered that 70% of parasitic nematodes host a large and diverse RNA virome (Quek et al. 2024, Nature Microbiology). We have focussed on a rhabdovirus, OVRV1, which is ubiquitous in endemic onchocerciasis populations and elicits antibody responses in infected or exposed communities. OVRV1 is phylogenetically related to lyssaviruses, including rabies, and as such may contribute to the disease pathogenesis of Onchocerciasis-Associated Epilepsy. To determine the fusogenicity and the resulting tropism of OVRV1 glycoprotein (gp) we have created lentiviral pseudotypes decorated with OVRV1 glycoproteins to define human cell susceptibility to infection. Pseudotyped lentiviruses provide an opportunity for rapid throughput to determine the functionality of putative viral glycoproteins, as well as provide mechanistic and tropism information in the absence of isolated infectious virus. To probe for cell susceptibility to OVRV1 gp-mediated entry, we exposed human cell lines of different origins (IRF3 KO lung epithelial A549 cells, embryonic kidney HEK293T cells and TZM-bl cells, a derivate of human cervix carcinoma HeLa cells) to GFP-encoding lentiviral particles decorated with OVRV1-gp. Subsequently, we quantified reporter expression two days post-transduction, with vesicular stomatitis virus (VSV)-gp pseudotypes used as positive control and rhabdoviral reference. Addition of OVRV1-gp lentiviral pseudotypes to cells generated GFP expression in a dose-dependent manner, providing robust evidence for the ability of OVRV1 gp to mediate entry into human cells and strengthening our hypothesis of OVRV1 infection-induced pathogenesis in humans. Current experiments are testing the susceptibility of human cell tropism of native OVRV1 and exposure to advanced human induced pluripotent stem cells (iPSC)-derived bi/tri-partite neurospheroid culture systems to determine OVRV1 infection of neural cells and tissues.

12 Virome of *Onchocerca volvulus* and its potential contribution to Onchocerciasis-Associated Epilepsy

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Using viral metagenomics and transcriptome analysis, we discovered a potentially pathogenic RNA rhabdovirus in *Onchocerca volvulus* (OVRV1). OVRV1 was detected in all *O. volvulus* life stages using PCR and immuno-histochemical microscopy. An OVRV1-glycoprotein based ELISA detected antibody responses against the glycoprotein in sera from exposed and infected individuals from onchocerciasis endemic foci in Uganda, Cameroon, Nigeria and Togo with seropositivity ranging from 93-100%. Onchocerciasis has been associated with epilepsy, onchocerciasis-associated epilepsy (OAE), but the pathogenesis of OAE remains to be elucidated. Nodding syndrome is one of the most disabling clinical presentations of OAE. I will summarise the epidemiological evidence that supports an association of OAE with high levels of onchocerciasis transmission required to develop nodding syndrome and provide examples of interventions with community directed distribution of ivermectin resulting in a decline or disappearance of nodding syndrome cases. Recently, a phase II trial using curative therapy with doxycycline in Ugandan patients with nodding syndrome demonstrated a decrease in acute seizure-related hospitalisation, decreases deaths related to nodding syndrome and substantially reduce in antibodies to *O. volvulus.* Future studies led by Dr Joseph N Siewe Fodjo funded by an European Research Council (ERC) grant will explore the potential clinical impact of the *O. volvulus* and *Mansonella perstans* viromes. The potentially pathogenic role of OVRV1 in OAE will be investigated by examination of cerebrospinal fluid and brain samples of cases and controls. In addition, in onchocerciasis-endemic areas of the Democratic Republic of Congo, South Sudan and Cameroon the effects of onchocerciasis and mansonellosis along with their respective viromes on pregnancy outcomes will also be explored.

13 Can fluke borne viruses contribute to cancer development?

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Metatranscriptomics analyses of parasitic helminths has revealed the existence of a hidden, diverse and abundant virome. Over 100 novel viral sequences have been identified in flatworms and an additional 91 in parasitic nematodes infecting humans and animals. Several virus-helminth associations are widespread covering multiple continents, suggestive of an ancestral acquisition event and host-virus co-evolution. Via chronic poly-parasitism and frequent re-infection, parasitic helminths have developed intimate and complex life-long associations with their hosts. This creates an environment which promotes direct exposure of multiple human tissues to helminth viruses and evidence for exposure to host immunity is found with high levels of sero-positivity to helminth-borne viruses. Parasitic helminth viruses may play a role in virus diversity and emergence. One example is the discovery of flatworm rhabdoviruses that have a position ancestral to rabies viruses and other vertebrate-associated rhabdoviruses, suggesting that vertebrate-associated rhabdoviruses emerged from a flatworm rhabdovirus in a parasitized host. The medical and biological relevance of these viruses is unknown, but extrapolation from viruses of protozoan parasites suggests potential roles in disease pathogenesis and other fundamental biological processes, which are critical knowledge gaps. To begin to address the influence of the helminth virome on the biology and pathogenicity of parasitic helminths we invite interested parties to join an interdisciplinary research network **VI-PAR** - Viromes of Parasites. COST (European Cooperation in Science and Technology) is a European funding organisation for research and innovation networks, funding interdisciplinary research networks called COST actions (deadline proposals: 21 October 2025). Duration of the project: 4 years. Objective: to boost research concerning virome studies in parasites through networking activities such as meetings, workshops, short-term scientific exchanges, conferences, training workshops and dissemination activities.

Rooting for resistance: Characterizing the NLR immune receptor network against root-knot nematodes in sweet potato

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Plants rely on their immune system to defend against pathogens, including plant-parasitic nematodes. Integral to this system are nucleotide-binding domain and leucine-rich repeat-containing (NLR) proteins, commonly referred to as resistance (R) genes. In Asterids, a large number of NLRs function in a network where “sensor” NLRs directly or indirectly detect pathogen effectors and “helper” NLRs induce downstream immune signalling. While well studied in Solanaceous plants, this system remains largely unexplored in *Convolvulaceae*, including sweet potato (*Ipomoea batatas*). The root-knot nematode (RKN) *Meloidogyne enterolobii* is an emerging threat to sweet potato, but how NLRs mediate resistance to RKNs remains unknown. We have recently delineated the phylogenetic network of NLRs in sweet potato using genomic and transcriptomic data and successfully characterized parts of the network. To identify NLRs important during RKN infection, we performed a dual transcriptomic study of sweet potato roots infected with *M. enterolobii* at early-stages of the infection. During compatible interaction, we found a concerted downregulation of several helper and sensor NLRs as early as 3 days post infection (dpi). In contrast, by 5dpi, more NLRs are upregulated than downregulated. Furthermore, most differentially regulated NLRs are unique to each time point. This coincides with distinct nematode effector expression profiles at 3dpi compared to 5dpi. Experiments to dissect the underlying regulatory mechanism of these differentially regulated NLRs and the corresponding effectors involved are underway, and latest findings will be discussed.

2 How and why plant-parasitic nematodes edit *HYP* genes in their somatic cells

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The *HYP* genes of plant-parasitic *Globodera* nematodes encode highly diverse secreted effector proteins. Recent work on *HYP*s strongly suggests that this diversity is allelic and that it is produced by developmentally-programmed rearrangements: that is, the nematodes edit *HYP* genes in their somatic cells by shuffling a set of short DNA sequence motifs within a hypervariable domain. Although the germline diversity of *HYP* alleles is small, such editing is thought to create hundreds or thousands of distinct somatic alleles across a population. Both the mechanism of *HYP* editing and its pathogenic function are unknown. In this talk, we present a DNA repair hypothesis for the mechanism of *HYP* editing, as well as an immune evasion hypothesis for its pathogenic function. We evaluate both hypotheses in light of the preliminary evidence available, with reference to a wide range of analogous editing systems in distantly related organisms.

Finding susceptibility in a resistance-breaking world

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California is the lead producer of processing tomato worldwide. The success of this industry depends on growers' abilities to implement management strategies such as integrated host resistance, effective pesticides, and non-host rotation crops to eliminate or control pathogens. Despite these efforts, root-knot nematodes (RKNs), *Meloidogyne* spp., cause an estimated 5% yield loss in processing tomatoes by suppressing the plant immune system, damaging root tissues, and creating entry points for secondary pathogens such as *Fusarium* species. These pathogen complexes result in a severe yield loss for growers each year. For decades, the resistance gene *Mi-1* has effectively detected and inhibited RKNs in tomatoes, but the underlying mechanisms by which it recognizes these pathogens remain largely unknown. However, resistance-breaking populations have been increasingly identified in both greenhouse and field settings, threatening the effectiveness of the *Mi-1* gene and consequently the tomato industry. To better understand how RKNs overcome Mi-1 resistance, we utilized two closely related strains of *Meloidogyne javanica*: VW4, a wild-type strain, and VW5, a lab-generated resistance-breaking strain. Through comparative genomics, we identified four nematode avirulent gene candidates that may interact with Mi-1. In addition, to assess the distribution of resistance-breaking RKNs and identify "hotspots" in California, we collected 14 field isolates from processing tomato fields across the state. These isolates are being confirmed to be resistance-breaking and are undergoing purification by single egg mass isolation. Confirmed resistance-breaking isolates will be used in infection assays on current rotation crops for processing tomatoes. With this research, we aim to improve understanding of how RKNs evade Mi-1 resistance and develop management strategies to combat these resistance breaking populations, ultimately supporting California's tomato growers.

Quantification of parasitic nematode feeding rates through stable isotope mass spectrometry

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Understanding feeding behaviors of plant parasites is crucial to determine the potential impacts on crop yield and quality, and provides avenues for novel control methods. Here, we employed the model root-knot (*Meloidogyne hapla*) and tomato pathosystem along with stable isotope labelling *in planta*. Coupled with high throughput mass spectrometry, this approach allowed for the temporal quantification of root-knot nematode feeding. Briefly, host plants were labeled using the stable isotope 15N as the sole nitrogen source during growth, as a continuous or 'spiked' supplement before inoculation with the parasite. Subsequent proteomic mass spectrometry of the parasite and infected tissue at different stages of its life cycle was used to calculate feeding rates based on the percentage of 15N labeling mapped back to the parasite and host genomes. Additionally, this approach allows for the identification of metabolic pathways utilized by the pest during feeding through differences in N15 enrichment in different amino acids and protein labeling. We demonstrate that nematode parasitism increases nitrogen incorporation by the host and identified potential targets for control both in time of nematode development and enriched pathways. Exposing host plants to both continuous and 'spiked' 15N, we achieved fold increases in labeling compared to background, which was sufficient to differentiate feeding rates and pathway enrichment for both the nematode and host tissue.

1 Unravelling interactions between populations of the intestinal stem cell niche that determine the initiation of immunity to whipworms

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Whipworms inhabit a unique multi-intracellular niche within the epithelium of the caecum of their hosts. Our previous work has shown that at early stages of infection, whipworm larvae tunnel through dividing cells at the crypt base, near the stem cell niche (SCN). The SCN comprises immune and stromal cells that influence stem cell fate. Initial interactions with whipworms are thought to drive intestinal epithelial cell (IEC) activation, which in turn initiates immune responses. However, IEC responses to whipworm invasion are poorly understood, and the mechanisms governing the crosstalk between infected IEC and SCN populations leading to the orchestration of immunity and IE repair remain elusive. Here, we investigated the responses and interplay of SCN populations during *Trichuris muris* acute infections of mice and caecaloids using imaging, FACS and transcriptomics. Temporal bulk-RNAseq experiments revealed that early responses to whipworm infection occur in orchestrated "waves" across SCN compartments. Transcriptomic changes are first observed at day 3 post infection (p.i), when IECs, and to a lesser extent stromal cells, exhibit a first response "wave" involving genes related to response to virus and antigen presentation. Surprisingly, we did not detect the expression of epithelial-derived alarmins (IL-25, IL-33, TSLP) suggesting responses to whipworms diverge from those to other helminths. At day 5 p.i., a second response "wave" from IEC and stroma cells leads to a type-1 immune response, which is joined by a "third" wave of type-2 immune responses and associated effector programs at day 8 p.i. To identify cellular populations behind these responses and their crosstalk, we have performed single-cell-RNAseq resulting in an "atlas" of half-million caecal cells under homeostasis and whipworm infection. Current analyses and validation experiments are uncovering the coordinated multicellular response and SCN remodelling processes that underlie the complex host's early defence and tissue repair mechanisms leading to whipworm expulsion.

2 Modelling host: parasitic nematode interactions with ovine 'mini-gut' organoids

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Teladorsagia circumcincta is one of the most predominant gastrointestinal (GI) nematodes of sheep in temperate regions. Reported resistance to anthelmintics is increasing and therefore research into new control strategies (e.g. vaccination) is vital. One area of interest for identification of potential vaccine candidates are extracellular vesicles (EVs). Extracellular vesicles are lipid membrane-enclosed packages which contain effector proteins and immune modulators and play important roles in establishing helminth infections. However, there are challenges in studying these interactions between the host and GI nematodes due to the lack of accessibility of the infection site and the need to rely on infection models which have ethical implications. Recently, ovine GI organoids have been developed which allow host-parasitic interactions to be studied in a physiologically-relevant and host-specific *in vitro* cell culture system. The overall aim of the project is to use ovine abomasum organoids to identify and characterise active components of *T. circumcincta* EVs at different infective life stages. The separation and characterisation of EVs from adult and larval stage 4 excretory/secretory products has been achieved. Protein characterisation of these EVs has revealed a consistency with proteins found in other nematodes (e.g. M13 metallopeptidases, actin) which further supports the presence of EVs. These EV proteins are also recognised by vaccinated and infected sheep when compared to controls. The development of apical-out ovine abomasum organoids has occurred which gives better access to the apical surface of the organoid and has allowed the visual confirmation of EV uptake by organoids. Further investigations are underway to look at the interactions and potential implications of these EVs at the host epithelial cell interface.

3 A reverse vaccinology approach to control scour worms in sheep

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Chemical drenches are the mainstay of parasite management of gastrointestinal nematode infections in livestock, but resistance to these treatments severely undermines control options on-farm and vaccination has been demonstrated to be a possible alternative. Trichostrongylid scour worms, *Trichostrongylus* and *Teladorsagia,* are not blood-feeding parasites so the "parasite gut antigen" approach used for *Haemonchus contortus* is unsuitable. Instead, vaccines need to be developed from analysis of naturally acquired immunity and host-parasite interactions. The project described here is a 5-year, multi-million-dollar project across 3 partners using and integrating current, multi-institutional expertise in small ruminant parasitology, immunology and vaccine formulation with activities in three major subprograms. The first subprogram establishes how acquired immunity is developed and operates early after parasites are ingested and established. We are now 2 years into this programme and have developed the serological, histological and transcriptomic tools and datasets required to understand the immunological effector landscape that we will need to recreate with a vaccine. The second subprogram focusses on antigen discovery, which determines which antigens are key to the generation of protective immunity against scour worms. This has involved the use/generation of chromosome-level genome assemblies for both species from which to produce datasets of predicted excretory protein antigens, alongside the transcriptomic and proteomic resources to verify and augment these predictions. From this combined resource of secreted antigen candidates, we have produced large-scale peptide arrays and probed them with immune sera from both parasite species. The data from these arrays, as well as the data from *in silico* predictions of antigenicity, stage-specific RNA and protein expression data, host-parasite interaction studies and RNAi screening data will be fed into the prediction of the best antigens. In the final subprogram**,** we determine the optimal vaccine formulations, combined with candidate parasite antigens, which will actually generate those protective responses in challenge studies.

18 Differential tissue destruction and inflammatory response in soil-transmitted helminth species among TB patients in the Peruvian Amazon

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Approximately 1.8 billion people worldwide are infected with soil-transmitted helminths (STHs), which are common in TB-endemic areas. TB-STH co-infected individuals have increased lung damage compared to those with TB alone. Matrix metalloproteinases (MMPs) are extracellular matrix-degrading enzymes that target collagen in the lung. The impact of individual STH species on TB-specific immune responses and on these mediators associated with tissue destruction is unclear. We recruited 61 adults with culture-confirmed pulmonary TB and 51 healthy controls (HCs) in Iquitos in the Peruvian Amazon jungle. Stool samples were examined for ova/cysts/parasites, and plasma was analysed for cytokine and MMP concentrations, and *Strongyloides* serology. Forty of 61 (66%) TB patients were STH-positive, compared with 22 of 51 (43%) HCs (adjusted OR 2.7, 95%CI 1.14-6.59). *Strongyloides* was the most frequently detected STH, followed by *Trichuris*, hookworm, and *Ascaris*. Both STH-positive TB and HC participants exhibited elevated pro-inflammatory cytokine and MMP concentrations compared to STH-negative participants. Due to the small number of STH-positive HCs, individual STH species-level data were analysed in TB-positive individuals only. Cytokines: IL-1β, IL-6, IL-12, IL-17, and TGF-β were significantly elevated in hookworm-positive participants compared to TB-positive, STH-negative individuals (TB+STH-). Only IL-17 was significantly elevated in *Strongyloides*-positive individuals. MMPs: MMP-10 concentrations were significantly elevated in all STH species, whereas MMP-13 was elevated only in hookworm-positive (873pg/mL, IQR 828-930) and *Strongyloides*-positive (853pg/mL, IQR 773-906) participants, compared to TB+STH- (766pg/mL, IQR 704-872, $p<0.05$). Only hookworm-positive TB patients had significantly elevated MMP-1 (5506pg/mL, IQR 3521-7311 vs 3052pg/mL, IQR 2282-4115, $p<0.05$) and MMP-8 (19,094pg/mL, IQR 9942-31,467 vs 9218pg/mL, IQR 6009-12,782, $p<0.05$). In summary, STH infection was associated with increased plasma cytokine and MMP concentrations, suggesting a mechanism for the exacerbated lung inflammation seen in TB-STH co-infection. Hookworm appeared to be the primary driver of these effects. These findings may inform targeted anti-helminthic strategies in endemic regions.

19 Investigating the relationship between kynurenine pathway and ivermectin resistance in *Dirofilaria immitis*

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The parasitic worm *Dirofilaria immitis* causes heartworm disease in dogs and poses a zoonotic threat to humans, making it a significant public health concern. Disease prevention relies on macrocyclic lactones (ML) such as ivermectin (IVM). However, the increasing prevalence of ML resistance has compromised disease control efforts. While genetic changes have been linked to ML resistance, the precise molecular mechanisms remain unclear. Unravelling these mechanisms is critical for maintaining effective disease control. Through metabolomic analyses, we discovered that drug-susceptible (SUS) isolates of *D. immitis* release higher levels of metabolites associated with tryptophan metabolism, particularly via the kynurenine pathway (KP), compared to drug-resistant (RES) isolates. On this study, we explore the relationship of KP and drug resistance in *D. immitis*. We employed real-time PCR to assess KP gene expression in *D. immitis* with and without IVM treatment. Our findings revealed that although *tryptophan 2,3-dioxygenase* (*tdo-2*) and *kynureninase* (*kynu*), two genes of KP, are highly expressed in RES isolates, their expression decreases upon IVM treatment. We then used *Caenorhabditis elegans* as a model organism to investigate the role of these genes in ML resistance. We performed larval development assays to assess the effect of IVM on different *C. elegans* strains carrying deletions in KP genes. Our results showed that the deletion of *tdo-2* increased susceptibility to IVM suggesting that the KP plays a role in drug resistance. These findings provide mechanistic insights into how KP regulation influences ML resistance in *D. immitis* and provide insights into novel drug targets.

20 Differential susceptibility of *Onchocerca ochengi* adult male worms to flubendazole in gerbils and hamsters

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Onchocerciasis is a devastating skin and eye disease that afflicts about 21 million people, most of whom live in sub-Saharan Africa. Its control with the microfilaricidal drug ivermectin is limited, thus necessitating the development of preclinical animal models to aid in the discovery of a macrofilaricide. Previously, we found that *Onchocerca ochengi* (the closest relative of the human *O. volvulus*) worm masses survive better in hamsters than in gerbils. The aim of this study was to compare the survival of *O. ochengi* adult male worms and their susceptibility to flubendazole (FBZ, a macrofilaricide) in gerbils and hamsters. The animals were intraperitoneally implanted with *O. ochengi* male worms, treated with FBZ, and sacrificed 35 days post-implantation. Unlike gerbils which had some worms moving freely in the peritoneum and some in newly formed nodules (neo-nodules), all the worms in the hamsters were found in neo-nodules. FBZ significantly decreased worm burden, motility, and viability in gerbils whereas it had no significant effect in hamsters. These results highlight a major difference in how *O. ochengi* adult male worms are sustained and affected by FBZ in gerbils compared to hamsters. Understanding the difference between these two models is important in the development of effective macrofilaricides for onchocerciasis.

21 The *Taenia solium* novel PA1 like protein homologue modulates the mTORC1 signalling, induces anti-inflammatory response while rewiring cellular metabolism

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Taenia solium, a helminth parasite causes Neurocysticercosis (NCC), which accounts for more than 70% acquired epilepsy cases in endemic regions. Its excretory secretory proteome (ESP) interacts directly with the host immune system. We did the proteomic analysis of ESPs and aimed to identify uncharacterised molecules which might have a potential role in the immunopathogenesis of NCC. Proteomic analysis revealed 247 proteins with both pro and anti-inflammatory nature and molecular weight ranging from 4kDa to 88kDa. In this work, we purified and investigated the role of one such molecule, the PA1. The relative mRNA expression analysis was done by qRT-PCR and protein levels were analysed with immunoblot assays. Further, internalisation assay for cellular localization of the protein was done. Changes in oxidative stress and glucose levels were determined through NBDG assay using flow cytometry. We also determined the protein stability through Molecular dynamics (MD) simulations and temperature sensitivity assay. The PA1 showed efficient internalisation and uniform distribution within differentiated macrophagic THP-1 cells. Protein internalization decreases glucose levels and reduces GLUT1 expression, a receptor for glucose transport in cells. Decreased glucose levels disrupt the mTORC1 signalling pathway decreasing the total mTORC1 complex which further reduces the oxidative stress and induces an inclination towards the anti-inflammatory response in the host. Bioinformatic evaluation revealed that PA1 shows a stable RMSD for 100 nanoseconds and remains stable over a range of temperatures in temperature sensitivity assay. Hence, PA1 plays a vital role in rewiring the cellular metabolism in differentiated THP-1 cells directly impacting the response of host immune system to *Taenia solium*.

22 Mechanistic modeling of helminth-malaria co-infections in mice

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Parasites often share their host with other species, leading to direct and indirect interactions between them. Co-infections between helminths and malaria parasites are widespread and it is well known that, depending on the species pair, this can result in worse outcomes for hosts. In addition, within-host interactions between parasite species can have knock on consequences for transmissibility, the prevalence of infection, and the evolutionary of traits underlying infection severity. Importantly, these interactions will change when one of the coinfecting species is targeted by control measures, potentially yielding unintended consequences for the severity, spread, or evolution of the non-target species. Predicting such off-target consequences requires a precise, mechanistic understanding of how parasites interact within hosts in the first place, but for many systems, this understanding is lacking. I will present our work modeling the within-host infection dynamics and interactions between the nematode, *Nippostrongylus brasiliensis,* and the malaria parasite, *Plasmodium chabaudi*, in experimental infections in mice. Perhaps as would be expected for a blood-feeding nematode, our model predicts that the background death rate of RBCs is higher in coinfections. However, we also find that outcomes depend on the initial dose of malaria parasites: at the highest dose, this influence of co-infection was not observed, suggesting that intraspecific competition between malaria parasites may overwhelm any effect of the worm. Such interactions between initial dose and co-infection, although difficult to predict a priori, are key to understanding variation in the severity of disease experienced by hosts and could inform studies of transmission dynamics in nature, where co-infection and low doses are the norm.

23Helminth-driven gut inflammation and microbial translocation are linked to altered vaccine responses in rural Uganda.

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Helminth-associated bystander effects at distal sites might result from gut mucosal damage and the associated translocation of microbial products into systemic circulation. We hypothesised that helminth-induced gut microbial translocation mediates, at least in part, immunomodulation of vaccine-specific responses. We used samples and data from 9-17-year-old participants of a randomised trial assessing effects of praziquantel treatment on vaccine responses in *Schistosoma mansoni* (*Sm*)-endemic rural Ugandan islands. Participants received BCG [week 0], yellow fever [YF-17D], oral typhoid (Ty21a), HPV [week 4], and tetanus-diphtheria (TD) vaccines [week 28]. We measured week 0 plasma concentrations of intestinal fatty acid binding protein 2 [I-FABP2], lipopolysaccharide binding protein [LBP], anti-endotoxin core antibodies [EndoCab] IgG and IgM, and soluble CD14 [sCD14], and week 8 faecal concentrations of lipocalin-2 [fLcn-2], occult blood [FOB], and calprotectin [fCAL]. Vaccine-specific responses were BCG-specific interferon-ɣ ELISpot responses and IgG responses to yellow fever-, typhoid-, HPV- (at week 8), tetanus- and diphtheria toxoid-specific antigens (at week 52). Linear regression was used to assess associations of gut inflammation and microbial translocation with baseline helminth infection, praziquantel treatment, and vaccine-specific responses. *Sm* was positively associated with fCAL and FOB, but inversely associated with sCD14. Hookworm was positively associated with I-FABP2, and infection with any helminth with EndoCab IgM, fCAL and FOB. Intensive praziquantel treatment reduced concentrations for all markers, significantly for fCAL and FOB. Associations of assessed markers with vaccine responses were predominantly inverse: BCG-specific response was inversely associated with fLcn-2, FOB, fCAL, LBP; yellow fever with fCAL; HPV with I-FABP2; and TD with sCD14. We show that *S. mansoni* drives gut inflammation and potentiates microbial translocation, that this effect is reversible with praziquantel treatment, and that gut barrier dysfunction might alter vaccine responses. Interventions to improve gut barrier function, and resulting consequences for vaccine responsiveness, should be investigated further.

24 Palladacycle Compound as a Potential New Drug Against Schistosoma mansoni

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Introduction: Human schistosomiasis, a neglected tropical disease caused by *Schistosoma* spp., affects over 72 countries due to poor sanitation. Praziquantel, the primary treatment, is effective against adult worms but less so against juvenile stages, with reports of reduced susceptibility in endemic areas. Thus, new treatment strategies are needed. Cysteine protease inhibitors have shown promise against *Trypanosoma cruzi*, *Plasmodium falciparum*, and *S. mansoni* in murine models. Palladacycle compounds (DPPE 1.1 and 1.2), particularly cathepsin B inhibitors, have demonstrated efficacy against *Leishmania amazonensis*. Given that cathepsin B, crucial for hemoglobin hydrolysis in *S. mansoni*, is a potential target, we aimed to characterize the *in vitro* schistosomicidal effect of DPPE 1.2.
Methods: Adult worms (males, females, and couples) and schistosomula were cultured with DPPE 1.2 (125-2000 nM) or DMSO (control) for 72 hours. Motility, viability (MTT and ATP assays), pairing, and egg-laying were assessed every 24 hours. Motility was scored from 0 (no movement) to 3 (complete activity). *In silico* molecular modeling with *S. mansoni* cathepsins and DPPE 1.2 was performed, followed by enzymatic inhibition assays using recombinant *S. mansoni* cathepsins.
Results: DPPE 1.2 significantly reduced adult worm motility in a dose-dependent manner, with males more affected than females. It also disrupted pairing, reduced egg-laying, altered egg development, and decreased schistosomula viability. The LD50 for schistosomula was low, indicating high potency. *In silico* modeling suggested DPPE 1.2 interacts with the cathepsin B1 catalytic site, supporting its inhibition as a mechanism of action. Enzymatic assays confirmed DPPE 1.2's inhibitory effect, particularly on cathepsin B.
Conclusions and Perspectives: DPPE 1.2 is a promising candidate for a new schistosomiasis drug. *In vivo* assays are necessary to validate these findings and will be the next step in our research.
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25 Parasitic pair: Uncovering the synergistic relationship between *Ancylostoma duodenale* and *Entamoeba histolytica* in a case of recurrent severe anaemia.

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Hookworm infections and amoebiasis remain major causes of morbidity and mortality in the developing world. Prevalence of both infections is highest in the tropics and subtropics, where poor hygiene, lack of access to potable water and unsanitary disposal of faeces predisposes people most especially those that reside in rural areas to these infections. Infections present with gastrointestinal symptoms such as abdominal pain and anaemia for hookworm infection while intestinal amoebiasis presents with passage of diarrhoeic or dysenteric stool which is foul smelling and abdominal pain. The following report describes a case of recurrent severe anaemia in a middle-aged tailor and peasant farmer, in whom the diagnosis of hookworm infection and intestinal amoebiasis was made. The patient underwent multiple blood transfusions for over a period of a year before referral to Obafemi Awolowo University Teaching Hospitals Complex, (OAUTHC), Ile-Ife for further evaluation. Endoscopy was done on the patient to exclude other causes of gastrointestinal bleeding but incidentally worms were found in the duodenal mucosa. This led to the examination of the stool sample of the patient which revealed the eggs of *Ancylostoma duodenale* and cysts of *Entamoeba histolytica*. The patient was subsequently managed with mebendazole and metronidazole at OAUTHC after exclusion of other possible causes of gastrointestinal bleeding. This case highlights the importance of considering parasitic infections as a cause of anaemia in the older age group, particularly where other critical differentials such as peptic ulcer disease and occult malignancy may result in delay in initiation of treatment and a significant financial burden on the patient.

26 The host gut microbiome alters chronic schistosomiasis-driven pathology

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Schistosomiasis affects over 251.4 million individuals globally, representing a significant global health challenge. Chemotherapy with praziquantel is the current most cost-effective approach for global disease control. Although PZQ can treat the infection and limit the associated morbidity, it does not prevent reinfection and the disease transmission persists in several endemic countries, yet the need for innovative strategies to manage the disease and its associated morbidity remains critical. Recent research revealed that schistosomiasis alters gut microbial composition, which could serve as a valuable tool for monitoring disease progression. This study investigates the intricate interactions between the host gut microbiota, host's genetic factors, and immune responses in the context of *S. mansoni* infection and its associated liver pathology. Here, we described for the first-time comprehensive gut metagenomics changes of school-aged children living in *S. mansoni*-endemic areas from rural Cameroon. Children were clustered according to the presence of schistosomiasis infection and/or liver fibrosis as a result of *S. mansoni* infection. Using shotgun sequencing, we revealed compositional and functional signature alterations in the gut metagenomes of individuals presenting with either schistosomiasis infection alone and/or associated pathology in the form of liver fibrosis, independently from their inter-individual genetic differences. Differential abundance testing revealed 17 microbial species with potential as biomarkers for *S. mansoni*-infection and/or liver pathology. These microbial species were further analyzed with quantitative PCR for validation of their potential as true biomarkers of *S. mansoni* infection and/or liver fibrosis. This research lays the groundwork for developing gut microbial biomarkers that could enhance monitoring strategies for schistosomiasis morbidity. By elucidating the relationship between gut microbiota alterations and schistosomiasis, we aim to contribute to more effective schistosomiasis management. The implications of our findings extend beyond mere diagnostics; they suggest a paradigm shift in how we understand and potentially influence schistosomiasis progression through microbiome modulation.

27 Developing a *C.elegans* System for Alzheimer's Drug Screening: Unveiling Phase Separation Dynamics via Multiphoton Imaging

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Neurodegenerative diseases, notably Alzheimer's disease, are significantly influenced by the biophysical properties of intrinsically disordered proteins (IDRs) such as tau. This study addresses the critical gap in in situ models for examining compounds that modulate phase separation of these proteins. Traditional screening methods predominantly rely on *in vitro* cell lines, which lack the comprehensive validation provided by *in vivo* systems. To bridge this gap, we developed a transgenic model of *Caenorhabditis elegans* expressing the human tau protein, engineered to include key phosphorylation sites vital for tau aggregation. Utilizing advanced molecular cloning techniques, including Gibson Assembly, we designed a robust plasmid vector equipped with strong regulatory elements, ensuring effective expression within the *C. elegans* system. Microinjection techniques facilitated the transformation of the standard N2 strain with the plasmid, leading to the successful establishment of transgenic lines. Employing novel multiphoton imaging (MPM) technology, we characterized the biomolecular condensates, visualizing tau protein localization in condensate using fluorescent markers. Validation of tau condensate formation was achieved through immunofluorescence and biochemical assays, revealing distinct properties associated with tau aggregation. Behavioral assays, including mobility tests, were performed to investigate the neurobiological consequences of tau expression in the transgenic model. The findings underscore the utility of the *C.elegans* model in studying tau-related pathologies, paving the way for screening biomodulators that could reverse dysregulation and potentially ameliorate neurodegenerative disease processes. This integrated approach not only enhances our understanding of tau's role in neurodegeneration but also provides a powerful platform for evaluating therapeutic compounds targeting these biophysical properties.

28 Development of an IgE-based reporter system essay for diagnosis of cystic Echinococcosis in dogs

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Introduction

Echinococcus sp. is one of the 20 Neglected Tropical Diseases (NTDs) targeted by the WHO for control and eradication. Clinical diagnosis mostly based on the presence of eggs (or proglottids) in faecal samples cannot morphologically be distinguished from frequently co-endemic *Taenia* sp. eggs. Copro-PCR and Copro-ELISA have shown good results, but rely on handling of potentially hazardous biological materials. Therefore, cheaper and safer tests such as serology would be an advantage. However, current serological tests based on IgG detection are unreliable due to low specificity.

Aim

Despite the central role of IgE responses in most metazoan parasite infections, this antibody isotype has not been used for diagnosis of Echinococcosis. We intend to develop a highly sensitive and specific serological assay by 'caninizing' rat basophil leukaemia (RBL)-derived IgE reporter cell lines for diagnosis of dog echinococcosis.

Materials & methods

Starting from an existing rat basophilic leukemia (RBL) reporter cell line (NPY-mRFP), which contains preformed red fluorescent proteins in granules, released upon activation, we developed three dog IgE reporter cell lines. Each cell line expressed a variant of the canine alpha chain of the high affinity IgE receptor (FcεRIα). The first construct encoded wildtype dog FcεRIα, the second expressed a chimeric dog/rat FcεRIα consisting of the extracellular FcεRIα dog sequence and the transmembrane/cytosolic rat sequence, and the third expressing a wild type dog FcεRIα chain in which three potential endoplasmic reticulum retention Lys signals have been changed to Ala. After several months of culture in the presence of a selective antibiotic, the cells were cloned by limited dilution using FACS. For functional testing, the cloned cells were sensitized with dog serum and polyclonal stimulation with an anti-dog IgE antibody.

Results

All three stable transfectants were put through clonal selection process. Several hundred clones were obtained, enriched and assessed for surface expression of dog FcεRIα by flow cytometry. Clones with the highest dog FcεRIα expression were expanded and tested for functionality. All three constructs sensitized with dog sera showed release of RFP reporter upon polyclonal stimulation with anti-dog-IgE, cross linking all surface-bound IgE. The released fluorescence was significantly increased compared to the parental cell line which did not express dog FcεRIα, while the signal to noise ratio between cell lines ranged between 2 and 3. Among the three cell lines the chimeric dog/rat cell line showed the highest RFP release.

Conclusion

We have successfully shown proof-of-principle that a rat-derived cell line is amenable to use with IgE contained in dog sera. However, the obtained signal to noise ratio of 2-3 is lower than expected and may result in a lack of sensitivity when used in combination with individual IgE binding antigens rather than the polyclonal stimulation used in this study.

29 *In silico* and *in vitro* charaterization of c-jun as a downstream player of the crosstalk between *S. mansoni* and host under human TNF-alpha regulation

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The trematode *Schistosoma mansoni causes* schistosomiasis in tropical and subtropical regions, including Brazil, affecting 200 million of individuals worldwide. The molecular crosstalk between helminths and their hosts is an important point to parasite development and reproduction. Previous studies by our group identified the human TNF-alpha receptor in *S. mansoni* and its homologs in helminths, highlighting the cytokine importance in parasite development, metabolism, and reproduction. *In silico* analyses revealed components of the TNF-alpha signaling pathway, including the transcription factor c-jun, which is crucial in embryonic development and reproduction across species like *D. melanogaster*, *C. elegans*, and flatworms *T crassiceps* and *T. solium*. Investigate and characterize the c-jun gene in *S. mansoni* and other helminths will help to elucidate important players in parasite-host signal transduction. Using BLAST, we compared the *S. mansoni* c-jun sequence (Smp_080420) with helminth genomes in WormbaseParasite17, supplemented by searches with the human sequence (NP_002219.1) and the HMMER algorithm. Conserved protein domains were identified using SMART and InterPro databases. Multiple sequence alignment and phylogenetic analysis were performed using MUSCLE and Mr.Bayes, respectively, using *Nematostella vectensis* as ancestor organism. Gene expression across developmental stages and sexes was analyzed using RNA-seq data, and c-jun binding sites were searched in differentially expressed genes in *S. mansoni* treated with TNF-alpha. We identified 77 c-jun homologs in helminths (26 flatworms, 51 nematodes), all with complete JUN and BZIP domains, confirmed by sequencing data. Phylogenetic analysis showed evolutionary separation between flatworm and nematode homologs. Differential expression was observed in miracidia, and single-cell RNAseq confirmed c-jun expression in cells involved in regeneration and neural tissue. C-jun binding sites in TNF-alpha-regulated genes suggest its role in gene regulation. These findings demonstrate c-jun conservation in *S. mansoni* and other helminths, with potential roles in development and regeneration.

30 Novel structure-activity relationships for nematicide benzamides

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Currently, there is an urgent need for new molecules with activity against parasitic nematodes for use in human, animal, and plant health. Benzamides constitute a novel family of nematicides that selectively inhibit complex II in these organisms. Fluopyram, a compound from this family, is already being used as an agricultural nematicide. Despite the extensive study of benzamides in recent years, no systematic exploration of the chemical space derived from nematocidal benzamides has been reported. We recently synthesized a library of 28 novel benzamide analogs designed according to five strategies: a) Bioisosterism of the amide group, b) *N*-alkylation, c) Rigidification, d) Modifications in the benzamide ring, and e) Hybridization with mitochondria-targeting groups. Additionally, the corresponding benzamides were synthesized, allowing for a direct evaluation of the effect of each design strategy. The compounds were preliminarily tested against *C. elegans* as a model nematode, allowing the elucidation of new structure-activity relationships for benzamide analogs. This work led to the identification of a new promising compound, **BI6b**, which was active against *C. elegans* and plant-parasitic nematodes of the *Meloidogyne* genus. Additionally, another compound (**BI4**), although not a nematicide, exhibited J2 penetration-preventing activity when evaluated *in planta*. This paves the way for the design of new compounds with phytonematode-repellent activities based on **BI4.** Furthermore, **BI6b** and its benzamide analog (Fluopyram) exhibited activity against flatworms, marking the first report of plathelminthicidal activity for this family of compounds. **BI6b** cytotoxicity was preliminarily assessed using murine fibroblast line L929. We are currently working on ecotoxicity assays. We are also studying the mechanism of action of **BI6b**, taking advantage of *C. elegans* genetic amenability.

31Targeting the DAF-12 signaling pathway for the treatment of strongyloidiasis

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Strongyloidiasis is a neglected tropical disease caused by the soil-dwelling parasitic nematode *Strongyloides stercoralis*. It affects approximately 30-100 million people globally with some estimates as high as 600 million people. Although acute strongyloidiasis is typically cleared by the immune system, chronic latent infection is common and can sometimes lead to the hyperinfection syndrome, which, if left untreated, has a mortality rate approaching 90%. Currently, the “gold-standard” treatment for strongyloidiasis is ivermectin, which, while effective at treating acute infection, does not prevent the development of chronic infection. This weakness of ivermectin is due to its inability to target the autoinfective larvae that are responsible for the continuous reinfection of the host. *S. stercoralis* contains a conserved developmental pathway known as the DAF-12 signaling pathway, which relies on the interaction between DAF-12, a nematode-specific nuclear receptor, and its steroid hormone ligand, Δ7-dafachronic acid, for the arrest and subsequent maturation of third-stage larvae (L3) into adult worms. Our laboratory has shown that pharmacologic inhibition of the Δ7-dafachronic acid producing cytochrome P450 enzyme Cyp22a9 with ketoconazole leads to arrested maturation of the L3s. Interestingly, ketoconazole and ivermectin work synergistically suggesting that targeting this pathway could potentially offer additional benefits in combination therapy. Unfortunately, because ketoconazole is a broad-spectrum CYP450 inhibitor, it is far too toxic for the treatment of latent *S. stercoralis* infections in otherwise healthy populations. For this reason, we are attempting to develop a novel pharmaceutical that can inhibit the DAF-12 pathway in a more targeted manner. Recently, our laboratory screened 10k compounds from a chemical compound library for the inhibition Cyp22a9. We have identified 25 lead compounds which are potent and specific inhibitors of Cyp22a9 and are non-cytotoxic. Further optimization of these lead compounds is ongoing.

32 The T-cell receptor repertoire of wild mice

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Wild animals' immune responses differ from those of laboratory animals because of the intense antigenic exposure that occurs in the wild. Comparing wild and laboratory mice shows that wild mice have comparatively elevated B and T-cell responses, but often reduced cytokine responses, presumably to ameliorate the potential for immunopathology that the high antigenic exposure would otherwise cause. T-cells play a central role in immune responses. Their activity is initiated by antigenic peptides of pathogens binding to T-cell receptors (TCRs), which are encoded by somatically recombined TCR genes. Each pathogen antigen is recognised by a small number of specific clones of T cells, so that individual animals have large, diverse repertoires of T cell clones. To further investigate the immune state of wild mice we determined the TCR repertoire of $CD4^+$ and $CD8^+$ cells of 65 wild mice. We did this by taking wild mouse splenocytes, separating $CD4^+$ and $CD8^+$ cells by flow cytometry, from which we prepared RNA, and then sequenced the TCRs' alpha and beta chain coding genes. We find that (i) wild mice have large TCR repertoires at a young age; (ii) $CD4^+$ and $CD8^+$ cells have similarly diverse TCRs; (iii) many TCR sequences are shared among mice, perhaps indicative of common infections in the sampled populations; (iv) there are relatively subtle differences between wild and laboratory mouse TCR repertoire size and diversity.

33 Evidence of ancient horizontal gene transfer in the human parasite *Schistosoma mansoni*

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Parasitic flatworms include some of nature's most successful and devastating pathogens. Schistosomes, for example, infect more than 2% of the world's population while other parasites such as tapeworms cause billions of dollars in economic losses every year. Despite having remarkably different physiology and ecological niches, all parasitic flatworms derive from a common ancestor and consequently share several common features. Many of these features, such as the presence of a protective syncytial skin-like tegument, are clearly adaptive; the schistosome's tegument allows the blood fluke to hide from the host's immune system while the tapeworm's tegument is responsible for nutrient uptake in these gutless animals. Other common features are not obviously adaptive: parasitic flatworms all lack the machinery required to produce piRNA, a class of small RNA responsible for repressing mobile genetic elements. While the exact consequences of the loss of piRNA are not known, it does suggest something of a 'wild west' with respect to how parasitic flatworms prevent mobile genetic elements from wreaking havoc on their genome. Our recent work identified a *cki* homolog that is ubiquitous throughout parasitic flatworms that appears to have arrived in parasitic flatworms by horizontal gene transfer (HGT) from an ancient metazoan host. We wondered if the lack of piRNA may have created an environment conducive to unusual genetic inheritance in the parasitic flatworms and set out to search for any other *S. mansoni* genes that may have arisen from HGT. By performing bioinformatic analysis, we were able to identify several genes that are absent from free-living flatworms but broadly present in parasitic flatworms as well as other organisms, suggesting that they may have arisen from HGT. Ongoing work is centered on studying these genes to better understand what, if any, role HGT played in the evolution of parasitic flatworms.

34 In Vitro Development of *Haemonchus contortus* from L3 Larvae to Egg-Laying Adults and Early Embryogenesis

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The hematophagous nematode *Haemonchus contortus* severely impacts global ruminant health, yet in vitro culture limitations hinder novel anthelmintic and vaccine development. Host coevolution has rendered *H. contortus* dependent on host-derived nutrients, which existing systems fail to replicate. We established a novel culture platform by identifying critical developmental factors. Using NCTC-135:LB (1:2) basal medium supplemented with 20% fetal bovine serum and 2.5% blood lysate, early L4 larvae achieved 76.04% survival. Enhanced supplementation (reduced glutathione, vitamin complexes, bovine liver extract) promoted 55.21% late L4 development by day 27, though molting to adults failed. Switching to SF insect medium enabled sexual maturation by day 32, with males producing sperm and females laying unfertilized eggs. Final additions (vitamin C, vitamin B12, Spermidine, Ecdysteroids) induced fertilization and embryonic progression to the four-cell stage. Although embryos did not fully develop or hatch, this system is the first to achieve stable cultivation of *H. contortus* from L3 larvae through adult maturation and early embryogenesis in vitro.. It offers a standardized model for studying gastrointestinal nematode biology and accelerating antihelminthic drug discovery.

1 The mechanisms generating new neurotransmitter receptors in nematodes and how to interpret diversity in multimeric proteins from an evolutionary perspective

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The pentameric ligand-gated ion-channels are major drug targets in the nematode parasites. They regulate neuronal signalling and muscle contraction throughout the animal kingdom. The major classes of pLGICs arose from a single gene inherited from the common ancestor with prokaryotes. This occurred rapidly as multicellular animal life appeared and movement can be identified from the Ediacaran epoch. Nematodes show a specific expansion of these receptor genes and variability in composition between even closely related species. We have used gene duplications that give rise to new receptors as a model to determine the mechanisms involved. We present evidence that new functionality arises rapidly, under selective pressure, revealing features important to new functions. Other features change progressively, likely due to random drift. Sequences within one subunit can determine its ability to interact with other subunits through a mechanism that is more specific than just a "bad fit". Position in a pentameric receptor evolves, and becomes fixed rapidly. Subunits can regulate their own compatibility and position in the receptor, they can also regulate other subunits not in physical contact. The requirement for accessory chaperone proteins can also change and they likely play a significant role soon after gene gain or loss changes subunit composition. This information will help to predict subunits that can combine when trying to identify novel drug targets and may lead to ways in which to manipulate receptor composition.

2 Pharmacological and computational profiling of a serotonin-responsive GPCR reveals a novel target for antiparasitic drug discovery

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Schistosomiasis affects over 250 million people globally, yet treatment relies exclusively on praziquantel (PZQ)—a single drug with emerging resistance and limited efficacy against juvenile parasites. To address this therapeutic gap, we are exploring bioaminergic G protein-coupled receptors (GPCRs), a validated but underexplored target class in schistosomes. Bioaminergic GPCRs regulate essential parasite behaviors, including motility and reproduction, and represent a promising avenue for next-generation anthelmintic discovery. Here, we present pharmacological and structural characterization of *Sm*.5HT$_{7b}$, a previously uncharacterized serotonin-responsive GPCR in *Schistosoma mansoni*. Using a real-time cAMP biosensor in CHO cells, we validated *Sm*.5HT$_{7b}$ as a functional serotonin receptor with selective activation by serotonin (EC_{50} = 400 ± 153 nM) and no response to other biogenic amines. We then constructed a high-quality homology model and performed *in silico* ligand docking, confirming canonical binding interactions of serotonin within the orthosteric binding site. These data enabled a preliminary pharmacological screen using a GPCR-targeted library of ligands aimed at characterizing the binding pocket of the receptor. To evaluate cross-species conservation, we extended our analysis to 5HT$_{7b}$ orthologs in *S. haematobium*, *S. japonicum*, *Clonorchis sinensis*, and *Fasciola hepatica*. Finally, we will present our results from a high-throughput virtual screen of *Sm*.5HT$_{7b}$ aimed at discovering new, parasite-selective ligands. Together, these efforts represent the first integrated pharmacological and computational profiling of *Sm*.5HT$_{7b}$. Our findings support this receptor as a viable drug target and (re)demonstrate the value in targeting bioaminergic GPCRs as anthelmintic targets.

3 Targeting nuclear hormone receptors in parasitic nematodes for effective parasitosis treatment

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Parasitic nematodes are responsible for several neglected tropical diseases infecting nearly three billion people worldwide and causing many disability-adjusted life years. Additionally, gastro-intestinal nematodes cause major economic loss in animal (livestock and domestic) industries. The control of these parasites relies mainly on drugs from the anthelmintic macrocyclic lactone (ML) family, with ivermectin (IVM) being the most used today in animals, and the gold standard parasiticide in humans. However, resistance to IVM and other MLs jeopardizes the success of nematode control in both animals and humans. There is an urgent need for new therapeutics to combat these infections. Nuclear hormone receptors, well-established therapeutic targets in mammals, have begun to be studied in parasitic worms, where they are widely distributed and play key roles in regulating metabolic and developmental transcriptional networks. Therefore, modulating nuclear hormone receptor signaling provides promising and innovative therapeutic opportunities. Our research aims to gain a fine understanding of the regulation of key nuclear hormones receptors, which are at the crossroads of major metabolic pathways in parasitic nematodes. To this end, we use a complementary set of biochemical, biophysical, structural, cellular and *in vivo* methods and we develop molecular tools, including synthetic ligands and peptides, to interrogate their biological functions and to develop new classes of inhibitors as candidate therapeutics. We will present recent exciting results about the development of such molecules.

4 Helminth-viral coinfection interactions in a wild rodent system

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Co-infection of hosts by multiple parasite and pathogen species is extremely common in nature, and many animals and humans harbour concurrent infections of helminths and pathogens such viruses, bacteria, and protozoa. Helminths can have significant effects on the host's immune system, potentially altering the host's ability to fight pathogen infections.
Unsurprisingly, this can lead to within-host interactions between the co-infecting species potentially resulting in the host having increased susceptibility, more severe pathology, enhanced transmission, and faster disease progression. We have established a hybrid wild/laboratory rodent model system in order to investigate the causes and consequences of coinfection in both controlled and wild conditions. Specifically, this work focuses on *Heligomosoides polygyrus* and its natural host, the wood mice (*Apodemus sylvaticus*), and addresses the following questions: (i) does chronic helminth infection increase susceptibility to Wood Mouse Herpes Virus (WMHV) in wild mice? (ii) is this interaction between helminths and viral susceptibility driving by changes in the immune response and (iii) using a controlle coinfection study in the lab, does coinfection impact both helminth and viral infection dynamics? Our results highlight how pairing both the lab and natural setting provides a unique and powerful opportunity to understand within-host coinfection interactions, specifically how chronic helminth infection can drive increased susceptibility and longer active viral infections in wild mice.

5 Elucidating Helminth-mediated Suppression of Anti-influenza Vaccination Efficacy

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Pre-existing helminth infections, afflicting more than a quarter of the human population, dampen the efficacy of vaccination, pivotal against life-threatening diseases like emerging viruses. We have shown before that infection with *Litomosoides sigmodontis*, a murine model for human filariasis, leads to reduced influenza vaccine-specific humoral responses, and increased viral load and weight loss upon challenge infection. Specific immune signatures that predict such a subpar vaccine response in helminth-infected individuals are lacking. This study aims to better understand how murine helminth infections impair vaccine responses efficacy in detail.

We first compared the suppressive capacity of two different helminth species: *L. sigmodontis* and the gastrointestinal nematode *Heligmosomoides polygyrus*. Helminth-infected and non-infected C57BL/6 mice were vaccinated using a commercially available adjuvanted anti-Influenza vaccine and the antibody response was measured by ELISA. Using spectral flow cytometry myeloid cells, innate lymphoid cell subpopulations as well as regulatory B and T cells and their expression of checkpoint molecules in different organs were analyzed.

Vaccination of non-helminth infected mice resulted in high influenza-specific IgG1, IgG2c, IgG2b and IgG3 titres. Comparison of the influenza vaccine specific Ab titres revealed a more robust suppression of all isotypes and more drastic changes of the cellular compartment by *L. sigmodontis* in contrast to *H. polygyrus*. We recorded differences in the cellular composition of lung cells and mediastinal lymph node cells in helminth infected mice, even after clearance of the infection, compared to non-helminth infected mice. In addition, preliminary data indicate reduced follicular T helper cells in the lung-draining lymph nodes in the presence of *L. sigmodontis* infection. We are currently trying to identify signatures from blood samples that correlate with vaccine-induced protection in naïve mice and failed protection in helminth-infected mice.

6 Enteric helminth infection impairs the memory T cell response to a recombinant vesicular stomatitis virus vector vaccine

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Vaccination relies on the induction of effective antibody responses, together with the priming and maintenance of long-lived antigen (Ag)-specific memory T lymphocytes. Gastro-intestinal helminths have been associated with reduced vaccine efficacy, through various immunoregulatory mechanisms. However, how helminth infection would impact the dynamics and response of memory T cells remains elusive. Here, we used both a recombinant vesicular stomatitis virus (rVSV) vector and an mRNA-based vaccine to investigate the memory T cell responses to the chicken ovalbumin (Ova) model Ag during enteric infection with the parasite nematode *Heligmosomoides polygyrus*. Naïve or *H. polygyrus* -infected mice were vaccinated at day 14 after infection with rVSV-Ova or mRNA-Ova intramuscularly. We observed a significant reduction of total, Ag-specific $CD8^+$ T cells and adoptively transferred Ova-specific OT-I cells in blood and spleen when vaccination occurred during helminth infection. To further investigate the response to vaccination during helminth infection, splenocytes at day 3 or 7 after rVSV-Ova administration were depleted of B cells, NK cells and neutrophils before single-cell (sc)RNA sequencing, including T cells, monocyte/macrophages and dendritic cells. While a cluster of *Cd4*-expressing T cells upregulated *Gata3, Cxcr6, Il4* and *Il1rl1* (T1/ST2) after *H. polygyrus* infection, a cluster of *Cd8a/Cd8b1*-expressing T cells upregulated effector/memory signature genes (*Gzmb, Cx3cr1, Klrg1, Itga4*) and was strongly enriched from day 3 to day 7 after vaccination. Strikingly, effector/memory $CD8^+$ T cells following vaccination of *H. polygyrus*-infected mice showed significantly lower enrichment, with reduced cytotoxic (*Gzma, Gzmb, Gzmk*) and activation (*Ccl5, Klrk1, Cx3cr1*) gene signatures. Finally, when challenged intratracheally with a murid gammaherpesvirus 4 recombinant strain expressing the OT-I epitope, vaccinated and *H. polygyrus*-infected mice showed a defective response in the lung of Ag-specific $CD8^+$ T cells and adoptively transferred OT-I cells. These results demonstrate that helminth infection impacts memory T cell responses and opens new avenues for mechanistic insights.

7 A history of hookworm infection protects mice against a pneumovirus-induced respiratory disease via recruitment of airway Ly6C^{+}CD64^{+} monocytes

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Helminths are known to regulate bystander inflammatory disorders, with several mechanisms still in discovery. In this study, we investigated the impact of helminth infection on immune control in a model of lethal viral pneumonia. BALB/c mice were infected with *Nippostrongylus brasiliensis*, a model of hookworm infection in mice. At 6 or 35 days after *N. brasiliensis* infection, mice were intranasally infected with a wild-type pneumonia virus of mice (PVM, strain J3666) or a recombinant virus expressing the luciferase gene (PVM-luc) to track viral replication over time by *in vivo* imaging. PVM belongs to the *Pneumoviridae* family and is a murine model for the closely related human respiratory syncytial respiratory virus (hRSV), a respiratory virus of medical significance in neonates, geriatrics, and immunosuppressed patients. Based on daily weight changes and viral bioluminescence measurements, we demonstrate that prior exposure to helminths protects against PVM-induced disease. Interestingly, protection was independent of both IL-4Rα and IL-5 signaling, as wild-type, IL-4Rα$^{-/-}$ and IL-5$^{-/-}$ mice were equally protected after helminth exposure. *N. brasiliensis*-mediated protection was associated with reduced neutrophils in the airway after viral challenge, and heightened Ly6C^{+}CD64^{+} monocyte recruitment to the lung. Depletion of CCR2^{+} circulating monocytes through administration of anti-CCR2 monoclonal MC21 antibody during early PVM infection resulted in a reduced recruitment of Ly6C^{+}CD64^{+} cells, and the loss of *N. brasiliensis* mediated protection against viral pneumonia. Thus, we demonstrate a determinant role of CCR2^{+} Ly6C^{+}CD64^{+} monocyte-derived cells in helminth mediated viral replication control, and in the regulation of PVM-associated detrimental inflammation.

8 Helminth-induced alterations of CD8$^+$ T cell immunity and its impact on colorectal cancer

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Parasitic helminth infections modulate host immunity by skewing immune responses toward a type 2 phenotype. This immunomodulation can attenuate Th1-driven inflammatory and autoimmune conditions but may also compromise host defense mechanisms against intracellular pathogens and tumors, or hinder immune protection induced by vaccination. To analyze whether a helminth infection interferes with type 1 immunity, the intestinal roundworm *Heligmosomoides (H.) polygyrus bakeri* was administered before tumor induction in a mouse model of colitis-associated colon cancer (CAC). Here, *H. polygyrus bakeri* infection enhanced the intestinal inflammatory immune response and significantly promoted the initiation and growth of tumors. *H. polygyrus bakeri* infection was accompanied by long-lasting alterations in the colonic immune cell compartment, including a reduced frequency of CD8$^+$ T cells. As cytotoxic CD8$^+$ T cells are crucial for mounting immune responses against tumors, we further analyzed the characteristics of CD8$^+$ T cells. We found that *H. polygyrus bakeri* infection significantly affected both the activation and proliferation of CD8$^+$ T cells in the colon and the mesenteric lymph nodes, independently of tumor development. *In vitro* studies further demonstrated that the restimulation of CD8$^+$ T cells from *H. polygyrus bakeri*-infected mice with a worm homogenate led to IL-4, IL-13 and IL-10 secretion, suggesting that these CD8$^+$ T cells have the potential to respond to helminth-specific antigens. Therefore, our study highlights that parasitic helminth infections have significant implications for cancer development and diseases in which host protection relies on CD8$^+$ T cell functionality.

9 Redundant and Nonredundant Functions of Group 2 Innate Lymphoid Cells during *Strongyloides ratti* Infection in Mice

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Strongyloides ratti is a rodent-specific parasitic nematode that displays tissue-migrating and intestinal life stages. Infections are controlled in the context of a type 2 immune response. While innate effector cells play important roles in reducing worm burden during the first week post-infection (p.i.), infection termination depends on the adaptive immune system. After a cleared infection, mice become semi-resistant to reinfections. This study aims to decipher the function of innate lymphoid cells (ILC2) during the infection with *S. ratti*. We use a novel mouse model targeting ILC2 in otherwise immunocompetent mice (Nmur1$^{iCre\text{-}eGFP}$) to analyze the role of ILC2 in the anti-*S. ratti* immune response. ILC2-deficiency increased numbers of tissue-migrating larvae day 2 p.i., intestinal parasite burden day 6 p.i., and larval shedding in feces, accompanied by reduced goblet and tuft cell hyperplasia, lower eosinophil levels, and decreased mast cell activation. However, infection clearance occurred with wild-type kinetics within one month. Notably, type 2 cytokine production and Th2 polarization were unaffected in ILC2-deficient mice. ILC2-derived IL-4/-13 were dispensable for controlling parasite burden, but caused a reduced tuft cell hyperplasia, indicating a dispensable role of tuft cell in controlling the parasite burden on day 6 p.i. In contrast, ILC2-specific deletion of IL-9 increased parasite burden on day 6 p.i. and resulted in a reduced mast cell activation, supporting IL-9´s described contribution to mucosal mast cell-driven parasite expulsion. During reinfection, intestinal parasite burden was comparable between ILC2-deficient and control mice. However, killing of tissue-migrating larvae day 2 p.i. infection was less efficient in ILC2 KO mice compared to control littermates. In summary, these results suggest that ILC2 and ILC2-derived IL-9 play a non-redundant role in controlling the initial parasite burden but ILC2 are dispensable for Th2 cell polarization and clearance of the infection. Ongoing studies are investigating the roles of ILC2-derived IL-5 and amphiregulin.

10 NET gains: AR restores neutrophils ability to kill Schistosomes via extracellular traps

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Schistosomes are helminths causing considerable global morbidity. The WHO aims to eliminate schistosomiasis as a public health problem by 2030, requiring novel interventions. The current drug of choice, praziquantel, displays low efficacy as a single dose and does not kill all parasite stages. The Aryl Hydantoin (AR) Ro 13-3978 is a leading candidate for a future schistosomicidal intervention: it works as a single dose, targets both juveniles and adult parasites and has a specific activity against Schistosomes. It had previously been established that ARs do not have direct schistosomicidal activity but instead have a host mediated mechanism likely through the immune system. We show by single cell sequencing that AR treatment activates Neutrophil Elastase in non-infected mice. We thus hypothesized that AR mode of action could be related to the release of Extracellular Traps (ETs) from granulocytes (large filaments of genomic/mitochondrial DNA decorated with toxic proteins, and released into the extracellular space). We show *in vivo* in a mouse model of *S. mansoni* that both neutrophil depletion and DNAse treatment reverse AR activity. Using an *ex vivo* co-culture system in which human polymorphonuclear neutrophils were exposed to worms and worm-derived products (ES), we show that schistosomes suppress NET formation. Strikingly, AR could restore this immune response, despite not triggering NETosis on its own. Proteomic analysis of human polymorphonuclear neutrophils treated or not with PMA/ AR and ES reveal that both ES and AR affect early decondensation of the chromatin, likely through modification of Histone 4 acetylation.

11 The transforming growth factor beta mimic (TGM) family of proteins from *Heligmosomoides polygyrus bakeri* target host dendritic cells to drive regulatory immune responses.

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H. polygyrus bakeri (*Hp)* excretory/secretory products (HES) contain a plethora of immune modulatory molecules which have evolved to manipulate the host immune response thereby securing long term parasite survival. *Hp* has convergently evolved a family of TGFβ mimics (TGMs) proteins which bind the host TGFβ receptors via their domains 1-3 and activate Smad2/3 signalling. We have previously demonstrated that *in vitro* HES suppresses the secretion of proinflammatory cytokines and expression of co-stimulatory molecules by bone marrow derived dendritic cells (BMDCs) in response to LPS. TGF-β signalling has an integral role in the development of CD103+ gut DCs and these DCs increase in frequency during Hp infection, as does their expression of markers associated with driving Treg responses. We aimed to investigate the role of the TGM family on the function of BMDCs. The TGM family is comprised of 10 secreted proteins which have varying degrees of homology to TGM1 and are distinct in their functional abilities to bind the TGF-β receptor, and whether they result in activation or inhibition of downstream signalling which is highly cell type specific and dependent on expression of co-receptors. Here we investigate the ability of TGMs to modify the functional response of BMDCs to toll like receptor (TLR) signalling. While TGM1, -4, and -7 reduced the secretion of proinflammatory cytokines, TGM6, which is inhibitory in fibroblast and epithelial cells, did not. We are now investigating the capabilities of TGM1, -4, -6 and 7 on pSmad2/3 signalling and the dependence of signalling on the CD44 and LRP1 co-receptors. These data suggest that, among other cell types, *H. polygyrus* TGMs target DCs to drive regulatory immune responses in their host and ensure parasite survival

Delegates at Hydra 2025

(Recipients of Travel Bursaries in Bold,
sponsored by **Merck Global Health Institute** and **New England BioLabs**)

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