Parasitic Helminths: New Perspectives in Biology and Infection

Hotel Bratsera, Hydra, Greece

Abstracts for Oral Presentations

5 September 2023

HYDRA ABSTRACTS TUESDAY 5 SEPTEMBER 2023

Tuesday 5 September

9:00 – 10:40 Session 4. Evolution and Ecosystems. Chair Amy Buck

09:00	Amy Pedersen	Edinburgh, UK	The ecological drivers of helminth infection and immunity in a lab-to-wild mouse model
09:40	Mark Viney	Liverpool, UK	Is *Strongyloides stercoralis* in people a zoonosis from dogs? – a whole-genome sequencing approach
10:00	Lewis Stevens	Wellcome Sanger, UK	Ancient diversity in host-parasite interaction genes in a model parasitic nematode
10:20	Grace Ajakaje	Adekunda, Nigeria	Proof-of-concept multilocus sequence typing scheme to investigate hybridization in *Schistosoma haematobium*

11:10 – 12:50 Session 5. Helminth Immunology. Chair Richard Grencis

11:10	Minka Breloer	BNITM, DE	CD160 regulates innate anti-helminth immune responses
11:30	Shinjini Chakraborty	York, UK	Chronic helminth infection alters bone marrow haematopoiesis via IL-4
11:50	Georgios Petrellis	Liege, BE	IL-4 receptor-α signaling regulates lung macrophages during helminth coinfection resulting in enhanced gammaherpesvirus permissiveness
12:10	Oyebola Oyesola	LPD/NIH, USA	Helminth exposure protects against murine SARS-CoV-2 infection through macrophage dependent T cell activation.
12:30	Dionysis Grigoriadis	EMBL-EBI, UK	WormBase ParaSite in 2023
13:00 – 14:00	WormBase Parasite Workshop		

16:00 – 17:40 Session 6. Type 2 Immunity. Chair Katie Smith

16:00	De'Broski Herbert	Pennsylvania, USA	Skin sensory neurons repel schistosomiasis
16:40	Pedro Gazzinelli-Guimaraes	NIAID/NIH	Decoding at single cell resolution the molecular and functional program of pathogenic Th2 cells subsets in humans
17:00	Xinxin Luo	Karolinska, SWE	Liver X receptor controls Tuft cell-ILC2 circuit impairing anti-helminth immunity
17:20	James Hewitson	York, UK	Platelet-immune cell cross-talk in the type 2 inflammatory response to *Schistosoma mansoni*

1) Is *Strongyloides stercoralis* in people a zoonosis from dogs? – a whole-genome sequencing approach

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It has been assumed that the parasitic nematode *Strongyloides stercoralis* transmits only among people. However, accumulating evidence suggests that *Strongyloides* from people and dogs are the same species, so that dogs can act as a source of human infection. To investigate the host range of *S. stercoralis* and the zoonotic potential of dog-derived *Strongyloides*, we sampled sympatric populations of worms from people and dogs in Bangladesh and in Thailand, which we then whole-genome sequenced. Population genomic analyses showed different genetic clusters of parasites, people in Bangladesh and Thailand were infected with closely related *S. stercoralis* genotypes, as too were infections of dogs in both countries. However, there was no evidence of *S. stercoralis* infections shared between people and dogs in Bangladesh or in Thailand. We are also using long-read analysis to better assemble human-derived *S. stercoralis*, and to study the diversity of their parasitism gene clusters that in *S. ratti* are hyperdiverse.

2) Ancient diversity in host-parasite interaction genes in a model parasitic nematode

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Host-parasite interactions exert strong selection pressures on the genomes of both host and parasite. These interactions can lead to the increased fitness of rare alleles, resulting in negative frequency-dependent selection, a form of balancing selection that is hypothesised to explain the high levels of polymorphism seen in many host immune and parasite antigen loci. Despite their economic and ecological importance, there is limited evidence for balancing selection in parasitism-relevant genes in parasitic nematodes. Here, we sequenced the genomes of several individuals of *Heligmosomoides bakeri*, a parasite of house mice that is a well-established model parasitic nematode, and its sister species *Heligmosomoides polygyrus*. We combined our single nematode genome assemblies with chromatin conformation capture (Hi-C) libraries derived from pools of individuals to generate chromosome-level reference genomes for both species. Despite a long-standing debate as to whether these two taxa belong to a single species, their genomes show levels of divergence that are consistent with millions of years of independent evolution. In addition, we found that the *H. bakeri* genome, which we expected to be highly homozygous, contains hundreds of hyper-divergent haplotypes, similar to those recently reported in free-living nematodes. Within these haplotypes, we found an enrichment of several gene families that are believed to interact with the host immune response, including protease inhibitors and transthyretin-like proteins. We also found that many of these haplotypes originated prior to the divergence between *H. bakeri* and *H. polygyrus* and have been maintained since their last common ancestor, presumably by long-term balancing selection. Together, our results suggest that selection pressures exerted on parasites by their hosts have led to unexpected modes and levels of genetic diversity in the genomes of these economically and ecologically important species.

3) Proof-Of-Concept Multilocus Sequence Typing Scheme to Investigate Hybridization in *Schistosoma haematobium*

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Schistosomiasis is a parasitic disease caused by blood flukes in the genus *Schistosoma* that infect human and animal hosts. Reports of ongoing hybridization between human and animal species of schistosomes in many parts of Africa suggest the existence of a species complex within the Schistosoma haematobium group, comprised of *S. haematobium*, *S. bovis*, *S. currasoni*, *S. intercalatum*, *S. guinnesis*, and *S. mattheei*.
As proof-of-concept, we developed a Nanopore multiplex amplicon sequencing (NMAS-Seq) platform based on newly identified markers to generate high-resolution data for studying schistosome genetic diversity. Using this concept, we investigated the presence of schistosome hybrids in four pastoral and non-pastoral communities in Nigeria. DNA was extracted from 119 parasite isolates obtained through urine filtration or from hatched miracidia. Multiplex nested PCR was used to amplify 12 markers, including rITS and mtCO1, and the amplicons were sequenced on the minION, and another 58 isolates were sanger sequenced. The sequence data was analyzed with Nanopolish, GATK, Geneious, and MEGA. In this study, all of the isolates had *S. bovis* alleles in at least two loci with varying levels of heterozygosity. Our multi locus sequence typing scheme detected *S. bovis* alleles in isolates that would have been tagged as pure *S. haematobium* based solely on mtCOX1 and rITS. The new markers provided additional inference on the diversity and population genetic structure within the complex group of schistosome species related to *S. haematobium*. Furthermore, we recorded a 99.9% agreement between our sanger and NMAS-Seq data with a 70% cost reduction for NMAS-Seq. We propose this multilocus typing scheme as an alternative for distinguishing between *S. haematobium*, *S. bovis*, and hybrids from both species.
Keywords: NMAS-Seq, Schistosomiasis, Hybridization, Species, Diversity, Nigeria

4) CD160 regulates innate anti-helminth immune responses

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Strongyloides ratti is a parasitic nematode that has tissue-migrating and intestinal life stages. Immunocompetent mice terminate infection within 2-4 weeks by a canonical type-II immune response. Termination of infection depends entirely on adaptive immunity, and RAG$^{-/-}$ mice lacking T and B cells remain infected for a year. Nevertheless, innate immunity is sufficient to reduce the intestinal parasite load from an initial level of approximately 80 parasites at day 6 p.i. to 2-5 parasites per mouse at later time points. CD160 is a regulatory receptor expressed on T cells, but also on cells of the innate immune system such as NK cells and ILC1. When comparing the parasite load of *S. ratti* in RAG$^{-/-}$ and RAG$^{-/-}$CD160$^{-/-}$ mice, we find a high and unchanged intestinal parasite load of approximately 50 parasites per mouse from day 6 to day 97 p.i. in the absence of CD160. Mucosal mast cells are the crucial effector cells mediating the ejection of *S. ratti* from the intestine. Accordingly, the intestinal mastocytosis and mast cell degranulation observed in *S. ratti*-infected RAG$^{-/-}$ mice was not present in RAG$^{-/-}$CD160$^{-/-}$ mice. Bm-derived WT and CD160-/- mast cells showed similar activation *in vitro*, ruling out an intrinsic effect of CD160 on mast cell activation. Early innate activation of mast cells during *S. ratti* infection is promoted by ILC2 in an IL-9-dependent manner. In addition to ILC1 and NK cells, we observed expression of CD160 on intestinal ILC2 *in vivo* that increased during *S. ratti* infection. Bm-derived CD160$^{-/-}$ ILC2 responded to *in vitro* stimulation with reduced IL-9 production compared with WT ILC2. Similarly, RAG$^{-/-}$CD160$^{-/-}$ mice did not show intestinal ILC2 expansion during infection *in vivo*, whereas intestinal ILC2 expanded in CD160-competent RAG$^{-/-}$ mice. In summary, our data suggest that CD160-mediated signalling contributes to ILC2 activation and ILC2-mediated innate immunity during intestinal helminth infection.

5) Chronic helminth infection alters bone marrow haematopoiesis via IL-4

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Hematopoietic stem cells (HSCs) respond to pro-inflammatory cytokines produced in response to infection or inflammation. Cytokines such as IL-1, TNF and both type-I IFN and IFNγ impair the function of HSC, though less is known about type 2 cytokines (e.g. IL-4, IL-5, IL-13). We used a murine model of chronic schistosomiasis to test the impact of type 2 responses on bone marrow (BM) haematopoiesis. Whilst IL-4 and IL-5 were elevated in the serum of chronically infected mice (12wks), IL-4 (but not other type 2 cytokines) was also increased in the BM of infected mice. Bulk RNA sequencing of immune progenitors (BM lineage- c-Kit+ Sca1+ LSK cells) revealed strong upregulation of transcripts associated with eosinophil differentiation, antigen presentation and, surprisingly, interferon stimulated gene signatures. Whilst infection led to increased proportions of all HSC and downstream multipotent progenitor populations, *in vivo* competitive transfers using lethally irradiated recipients showed these expanded cells had poor engraftment potential, revealing reduced functionality. Many of these changes are maintained after curative praziquantel treatment. To investigate potential mechanisms of infection-induced HSC changes, we performed single cell *in vitro* assays with individual HSC. IL-4 accelerated early expansion which was associated with greater differentiation and ultimately reduced cell survival. In addition, IL-4 modulates HSC changes induced by pro-inflammatory cytokines such as IFNγ. *In vivo* transfer experiments showed IL-4 treated HSC to have reduced myeloid engraftment potential. Together, we find type 2 responses in chronic schistosome infection promote HSC differentiation and reduced functionality. Ongoing experiments are focused on determining the extent and persistence of HSC changes, as well as the downstream consequences for mature immune cell function in both schistosomiasis and unrelated challenges.

6) IL-4 receptor-α signaling regulates lung macrophages during helminth coinfection resulting in enhanced gammaherpesvirus permissiveness

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Parasite nematodes, like hookworms, migrate through the lung and could condition how tissue macrophages respond to subsequent respiratory viral coinfections. Comparison of the innate immune cell populations in the lung of *Nippostrongylus brasiliensis* (Nb)-infected BALB/c and C57BL/6 mice revealed pronounced phenotypic changes in lung macrophages that were associated with an increased type 2 airway inflammation in C57BL/6 mice. These changes consisted of a disappearance reaction of SiglecF^{+} alveolar macrophages (AlvMs) and concomitant recruitment of CD11b^{+} macrophages that accumulated in the lung and airways. Using *Ms4a3*^{TdT} reporter mice, we demonstrated a monocytic origin of CD11b^{+} macrophages, which were phenotypically distinct from AlvMs. Using *in vivo* antibody-mediated IL-13 blockade and WT:*Il4ra*$^{-/-}$ bone marrow mixed chimeras, we found that IL-4/IL-13 macrophage signaling was required for the observed phenotypic changes in lung macrophages during Nb infection. When Nb-exposed C57BL/6 mice were infected intra-tracheally with murid gammaherpesvirus 4 (MuHV-4), we observed severely increased levels of acute replication in the lung compared to mice that had not been exposed to the parasite. MuHV-4 has a natural tropism for AlvMs *in vivo* and we observed an increased permissiveness restricted to AlvMs and monocyte-derived macrophages in coinfected mice. The observed increased permissiveness was not observed in *Il4ra*$^{-/-}$ mice, suggesting that the IL-4/13-dependent lung macrophage changes observed during Nb infection might explain the increased viral permissiveness. Interestingly, intra-tracheal instillation of recombinant IL-4 or IL-13 reproduced the observed macrophage changes after Nb infection and enhanced permissiveness to MuHV-4. Finally, we found that airway macrophages isolated from Nb-infected C57BL/6 mice were more permissive to MuHV-4 infection *ex vivo* and that IL-4 and IL-13 could potentiate macrophages permissiveness to MuHV-4. In conclusion, we propose that type 2 inflammation, during Nb infection, causes phenotypical and functional Il4ra-dependent restructuration of the airway and lung macrophage populations, significantly increasing their permissiveness to gammaherpesvirus coinfection.

7) Helminth exposure protects against murine SARS-CoV-2 infection through macrophage dependent T cell activation.

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Helminth endemic regions report lower COVID-19 morbidity and mortality. Here, we show that lung remodeling from a prior infection with a lung migrating helminth, *Nippostrongylus brasiliensis*, enhances viral clearance and survival of human-ACE2 transgenic mice challenged with SARS-CoV-2 (SCV2). This protection is associated with a lymphocytic infiltrate including an increased accumulation of pulmonary SCV2-specific CD8+ T cells and anti-CD8 antibody depletion abrogated the *N. brasiliensis*-mediated reduction in viral loads. Pulmonary macrophages with an altered transcriptional and epigenetic signature persist in the lungs of *N. brasiliensis* exposed mice after clearance of the parasite and establish a primed and trained environment for increased antigen presentation and recruitment of CD8 T cells. Accordingly, depletion of macrophages ablated the augmented viral clearance and accumulation of CD8+ T cells driven by prior *N. brasiliensis* infection. Together, these findings support the concept that lung migrating helminths can limit disease severity during SCV2 infection through macrophage-dependent enhancement of anti-viral CD8+ T cell responses.

WormBase ParaSite in 2023

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WormBase ParaSite (WBPS) is a comprehensive resource for nematode and platyhelminth genomics. Advances in genome sequencing technologies have enabled WBPS to host more genomes than ever before, with an increasing number of high-quality reference assemblies. Structural gene annotation and gene descriptions have been improved as well, with more genome projects using long-read RNA-Seq data to assist their gene prediction algorithms. However, there is a growing problem of disparity in quality, when older projects are analysed alongside newer ones. In many cases, genome projects could be significantly “upgraded” with newer methods and experimental evidence, but this ongoing maintenance creates a curatorial backlog. Even when new projects can simply replace older ones, it’s critical that published information is forward-tracked between versions.

In this workshop, we will showcase the strides WBPS has made in incorporating primary genome annotations and updates from the research community. We will discuss new approaches to upgrade annotations that include scalable automated approaches as well community contributions garnered through the web-based Apollo interfaces.

We will also demonstrate new features of the site for exploring individual gene/protein function. 3D protein models from AlphaFold have recently been fully integrated and are presented via an interactive widget. Similarly, gene-phenotype associations have been imported for *C. elegans* and *S. mansoni*, and are now propagated via orthology to all genomes. Our comparative analysis tools have been enriched with new pairwise whole genome alignments presented with a new viewer, while our traditional online tools (BLAST, VEP and gProfiler) have had updates.

WormBase ParaSite remains dedicated to improving its services, in the face of a challenging funding environment. To do this, it’s more important than ever that we focus effort where it’s most needed in a rapidly evolving field of worm omics. We, therefore, encourage you to share use-cases and participate in discussions about improvements and make suggestions for areas to prioritise.

9) Decoding at single cell resolution the molecular and functional program of pathogenic Th2 cells subsets in humans

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Unraveling the diversity of Th2 cells may help us to understand their pathogenic role in Type-2 associated inflammatory disorders, including helminth infections and allergies. To characterize the heterogeneity and function of these effector Th2 cells, we analyzed 47 subjects' PBMCs [23 filarial-infected (Fil^+) and 24 healthy volunteers (Fil^-)], with or without coincident house dust mite (HDM)-allergic sensitization (Fil^+HDM^+ n=12; Fil^+HDM^-, n=11) and (Fil^-HDM^+ n=12; and Fil^-HDM^-, n=12) using multiparameter flow cytometric two-level clustering analysis. The frequency of 3 memory $CD4^+$ T cell clusters, including $CCR4^+CCR6^+CRTH2^-$ (subset 1), $CCR4^+CCR6^-CRTH2^+$ (subset 2), and $CCR6^+CCR4^+CRTH2^+$ (subset 3) were markedly enriched among Fil^+ subjects. Functional characterization indicated that subsets 2 and 3 together were responsible for the majority of IL-4, IL-5, or IL-13 produced among the Fil^+ subjects. These 2 subsets were sorted and analyzed by multiomic single cell RNA profiling. Both subset 2 and subset 3 had features of pathogenic Th2 effector (PeTh2) cells based on their molecular signature, including downregulation of *cd27* and high expression levels of *itga4, il-17rb, hpgds, klrb1, ptgdr2, il-9r, il-4, il5 and il-13* genes. When the Fil^+ subjects were subdivided based on allergic status, the Fil^+HDM^+ subjects had an expansion in the frequency of both Th2 cells subsets when compared with the Fil^+HDM^- subjects. Gene expression analysis further demonstrated that HDM sensitization concomitant with filarial infection reshaped the molecular program of these PeTh2 subsets by even further upregulating the expression of *gata3, il17rb, clrf2, and klrb1*. Notably, Fil^+HDM^+ patients' cells showed higher responsiveness to filarial or HDM antigen stimulation, with induced levels of IL-4, IL-5, and IL-13 significantly higher than those induced in the Fil^+HDM^- patients. This distinct molecular and functional program of Th2 effector cell subsets sheds new light on the Th2 cell plasticity and their contribution to immune regulation in helminth infection and allergies.

10) Liver X receptor controls Tuft cell-ILC2 circuit impairing anti-helminth immunity

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Dietary components play vital role in shaping our intestinal mucosal immunity. Among dietary compounds, cholesterol metabolites, oxysterols, bind and activate the Liver X Receptors (LXR) triggering quick responses to enable immune adaptation. Despite extensive research on the immune regulatory effects of LXR, its role in regulating interactions between hosts and helminths remains ambiguous. Here, we examined the role of LXR on host response during *Heligmosomoides polygyrus bakeri* (*Hpb*) infection. We found that mice fed with LXR agonist, GW3965(GW) led to decreased type 2 innate lymphoid cells (ILC2) and tuft cells number in the small intestine. Impaired ILC2 function was rescued by exogenous administration of rIL-25 *in vitro*, indicating that LXR does not affect ILC2s directly. Conversely, exogenous succinate failed to rescue the LXR-mediated decreased tuft cells in number, suggesting that succinate sensing by tuft cells is influenced. Upon exposure to the succinate-independent *Hpb* infection, GW-treated mice showed reduced tuft cell numbers at 14dpi compared to the control diet group, suggesting that LXR disrupts the tuft cell-ILC2 loop. In line with the role of the tuft cell-ILC2 circuit in anti-helminth response, we observed enhanced worm fecundity and reduced mast cell activity in GW-treated mice compared to the control. Using spatial transcriptomic analysis we identified that *Hpb* granuloma locally induced a unique stem cell reprogramming process at 6dpi which manifested as a fetal-like growth. However, LXR activation preserved the adult regeneration program in intestinal crypts. Collectively, our study has evidenced the involvement of LXR in regulating tuft cells and influencing both host defense and stem cell reprogramming during helminth infection.

11) Platelet-immune cell cross-talk in the type 2 inflammatory response to *Schistosoma mansoni*

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Beyond their role in haemostasis, platelets are strongly immunomodulatory in type 1 inflammatory responses to bacteria and viruses. However, the role of platelets in type 2 responses characteristic of helminth infection is less well understood. Despite their large size (~1cm), intravascular adult *Schistosoma mansoni* worms do not cause coagulation and previous studies have shown parasites modulate platelet activation. Our aim here was to assess both haemostatic alterations and platelet-immune cell crosstalk in a mouse model of schistosomiasis. We found chronic schistosome infection induces thrombocytopenia that persists even after drug-mediated worm clearance. This is associated with marked reductions in circulating thrombopoietin (TPO) levels, coincident with extensive liver damage and loss of TPO-producing hepatocytes. Despite this, bone marrow megakaryocyte (MK) numbers were unchanged and infection instead caused elevated spleen and liver MK. Surprisingly, whole blood aggregometry showed platelets from schistosome-infected mice spontaneously aggregate in the absence of exogenous agonists, and whilst these platelets lack an activated phenotype, liver transcriptomic datasets show a hypercoagulable signature. To investigate platelet-immune cell interactions, we developed a novel *in vivo* platelet-tracking technique. This revealed enhanced platelet clearance by splenic and liver macrophages in infection, which occurs in an FcRγ-independent manner. Platelets are preferentially taken up by an expanded Ly6C(lo) MHCII(lo) RELMα(+) liver macrophage subset. We used *in vitro* longitudinal live cell imaging to test whether platelets modulate macrophage function. This showed platelets enhance the phagocytic ability of type 2 macrophages without impacting on markers of alternative activation (RELMα, Ym1). Both platelet-depleted and platelet-deficient mice quickly succumb to infection with extensive bleeding and bone marrow failure, highlighting the essential role of platelets preventing severe disease. Together, our studies reveal schistosome-induced haemostatic disruption alongside platelet-mediated immunomodulation of type 2 immune cells. We are currently using pharmacological approaches to boost platelet levels in schistosome infection and determine the immunological consequences.