Parasitic Helminths: New Perspectives in Biology and Infection

Hotel Bratsera, Hydra, Greece

Abstracts for Oral Presentations

7 September 2023

Thursday 7 September

9:00 – 10:40 Session 10. Helminth Development. Chair Jim Collins

09:00	**Tania Rozario**	**Athens, Georgia, USA**	**Understanding signals that regulate stem cells and germ cells in the regeneration-competent neck of the rat tapeworm, *Hymenolepis diminuta***
09:40	David Mangelsdorf	Texas, USA	The nuclear receptor paradigm of infection in parasitic nematodes
10:00	Christoph Grevelding	Giessen, DE	Single-cell transcriptomics of *Schistosoma mansoni* oocytes identifies a retinoid acid receptor essential for meiosis entry, zygote development, and egg formation
10:20	Jan Dvorak	Czech University	Egg-cellent insights: Transcriptomic analysis of *S. mansoni* egg development – winners vs. losers

11:10 – 12:50 Session 11. Immunomodulation. Chair Minka Breloer

11:10	Thomas Nutman	NIAID/NIH	A filarial parasite-encoded IL-5 antagonist suggests a novel strategy used by helminths to modulate host responses
11:30	Shashi Singh	Glasgow, UK	Transforming growth factor beta (TGFβ) mimic 4 (TGM4) of *Heligmosomoides polygyrus* targets myeloid cells through TGFβ receptors and multiple coreceptors
11:50	Katherine Smith	Cardiff, UK	Greedy Worms: manipulating PUFA metabolism to survive and influence host immunity
12:10	Peter Nejsum	Aarhus, DEN	*Ascaris suum* extracellular vesicles target human monocytes to generate a unique phenotype affecting T-cell anergy
12:30	Clarissa Prazeres da Costa	Munich, DE	Helminthic glutamate dehydrogenase-dependent PGE2 production in monocyte and microglia potentiates Treg development with distinct transcriptional profiles

16:00 – 18:00 Session 12 Non-coding RNAs. Chair Dick Davis

16:00	**Vicky Hunt**	**Bath, UK**	**The role of secreted exosome-like vesicles in parasite-host interactions and potential as a biomarker in *Strongyloides* infection**
16:40	Murilo Amaral	Sao Paolo, BRA	Schistosomal extracellular vesicle-enclosed long non-coding RNAs are transferred to the mammalian host

17:00	Amy Buck	Edinburgh, UK	RNA communication in helminth-host interactions

1) The Nuclear Receptor Paradigm of Infection in Parasitic Nematodes

Zhu Wang[1], Mi Cheong Cheong[1], Yanjie Liu[1], James B. Lok[2], Steven A. Kliewer[1], and **David J. Mangelsdorf[1]**

[1]Department of Pharmacology and Howard Hughes Medical Institute, U.T. Southwestern Medical Center at Dallas, Texas; [2]Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA.

The ability to regulate nutrient metabolism in both fed and fasted states is a physiologic process that coincided with the evolution of nuclear receptors in all multi-cellular organisms. In nematodes, we have discovered an orthologous pathway mediated by the nuclear steroid hormone receptor, DAF-12, and shown that it functions as the requisite developmental switch governing developmental arrest at the dauer-like infectious stage. Our characterization of the DAF-12 ligands and their biosynthetic pathways in species ranging from mammalian to plant parasites has revealed a remarkably conserved paradigm of infection that is unique to nematodes. Importantly, we have shown that therapeutically targeting different components of the DAF-12 pathway offers an unprecedented anthelmintic strategy.

2) Single-cell transcriptomics of *Schistosoma mansoni* oocytes identified a retinoid acid receptor essential for meiosis entry, zygote development, and egg formation

CHRISTOPH G. GREVELDING[1], ZHIGANG LU[1,2], CARMEN DIAZ SORIA[2], THOMAS QUACK[1], GABRIEL RINALDI[2,3], NANCY HOLROYD[2], MATTHEW BERRIMAN[2,4], MAX MÖSCHEID[1]

[1] INSTITUTE FOR PARASITOLOGY, JUSTUS LIEBIG UNIVERSITY GIESSEN, GERMANY; [2]WELLCOME SANGER INSTITUTE, WELLCOME GENOME CAMPUS, CB10 1SA CAMBRIDGE, UK; [3]DEPARTMENT OF LIFE SCIENCES, ABERYSTWYTH UNIVERSITY, PENGLAIS CAMPUS, ABERYSTWYTH SY23 3DA, WALES, UK [4]WELLCOME CENTRE FOR INTEGRATIVE PARASITOLOGY, INSTITUTE OF INFECTION, IMMUNITY & INFLAMMATION, COLLEGE OF MEDICAL,VETERINARY & LIFE SCIENCES, UNIVERSITY OF GLASGOW, 120 UNIVERSITY PLACE, GLASGOW G12 8TA, UK

Remarkably, the *Schistosoma* female parasite achieves sexual maturation only if constantly paired with a male partner. Although the male is sexually mature before pairing, male-female interaction appears to be bidirectional. Except for few genes known to regulate female sexual reproduction, our understanding of the complexity of pairing-dependent gene expression in the gonads remains limited. Based on an organ-isolation protocol for *S. mansoni* and subsequent transcriptomics, we previously identified transcripts of >7,000 genes in the gonads of both sexes. Among these, transcripts of 3,600 ovary-expressed genes showed differential regulation after pairing. Of these, 309 genes additionally revealed ovary-specific expression.

Here, we performed single-cell transcriptomics with cell suspensions collected from ovaries isolated from paired (bF) and unpaired (sF) females. Similar to our previous findings, we detected transcripts of a total number of 8,337 genes in all cells. After data filtration, we obtained 1,967 cells expressing 7,872 genes for clustering analysis. In the bF ovary, we detected four distinct clusters, whereas oocytes of sF ovaries were uniform, representing a single cluster. We identified a retinoid acid receptor (RAR) ortholog, expression of which is pairing-dependent in mature oocytes. Functional characterisation by RNAi and inhibitor treatment showed a complex, reproduction-associated phenotype suggesting roles of the RAR gene in meiosis entry, zygote development, and egg formation.

The novel sub-transcriptomics data set provided complements existing *omics* data for *S. mansoni* and provides a useful basis for studies on genes that are involved in the pairing-dependent sexual maturation of females and egg production. Since the eggs are not only essential for life-cycle progression, but also key drivers for the pathogenesis of schistosomiasis - which is the infectious disease caused by schistosomes - research focusing on reproduction may lead to novel and urgently needed control strategies.

3) **Egg-cellent insights: Transcriptomic analysis of *S. mansoni* egg development – winners vs. losers**

Kristyna Peterkova[1,2], Lukáš Konečný[1,2], **Jan Dvorak[2,3]**

[1] Department of Parasitology, Faculty of Science, Charles University, Prague, Czechia; [2] Centre for Infectious Animal Diseases, Czech University of Life Sciences, Prague, Czechia;[3] Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences, Prague, Czechia

The eggs of *Schistosoma mansoni* cause severe pathology in the host tissues. While immature eggs are immunologically inert, mature eggs actively induce inflammatory processes to pass from the endothelial tissue into the gut environment, causing granuloma formation. Many eggs are washed out from mesenteric veins mostly to the liver, where granuloma formations cause significant pathologies. The excretory/secretory products of eggs are known to play a crucial role in these processes, but their specific roles and molecular composition are not fully understood. So far, most of the attention has been devoted to egg-specific glycoproteins IPSE-1/alpha-1 and omega-1, among others, which promote Th2 polarization. However, the entire molecular composition of egg secretome and the roles of particular molecules remain unresolved.

To address this knowledge gap, we combined transcriptomic analysis and biochemical approaches to analyze a portfolio of molecules produced by *S. mansoni* eggs. We focused on developed and undeveloped eggs isolated from gut and liver tissues to identify potential differences in their inflammatory reactions. Our data revealed that gene expression is critically dependent on the developmental stage and tissue localization of the eggs. In addition to the crucial differences in expression between eggs derived from the two tissues, we found that the expression profiles of liver-derived eggs are very similar regardless of their developmental stage, whereas gut-derived eggs show remarkable changes during their maturation. Importantly, we identified several groups of highly abundant proteins whose presence is often stage and tissue-localization dependent, including the micro-exon gene (MEG) protein family and venom allergen-like (VAL) proteins. Interestingly, our study found that IPSE/alpha-1 and omega-1, often discussed as the primary weapons during Th2 inflammatory processes, are almost restricted to liver eggs. Conversely, the up-regulated molecules in gut-derived eggs, which attach themselves to the cell wall, probably represent the tools for successful passage to the external environment. We argue that such differential expression of many important groups of molecules directly reflects the environment in which the *S. mansoni* egg is located.

4) A filarial parasite-encoded IL-5 antagonist suggests a novel strategy used by helminths to modulate host responses

Thomas B. Nutman[1], Gnanasekar Munirathinam[2], Sasisekhar Bennuru[1], Alessandra Ricciardi[1], Rojelio Mejia[1], Sara Lustigman[3], YaeJean Kim[1], Pablo Bara-Garcia[1], Pedro Gazzinelli-Guimaraes[1], and Ramaswamy Kalyanasundaram[2]

[1]Laborartory of Parasitic Diseases, NIAID, NIH, Bethesda, MD (USA)
[2]Department of Biomedical Sciences, College of Medicine, University of Illinois, Rockford, IL (USA)
[3]Lindsay F. Kimball Research Institute, New York Blood Center, New York, NY (USA)

Peripheral blood and tissue eosinophilia occur early following infection with tissue invasive helminth parasites, and interleukin-5 receptor (IL-5R) signaling largely drives this response. A molecule we termed *Brugia malayi* (Bm) IL-5R binding protein (BmIL5Rbp now renamed Bm8757b) was identified originally through panning a Bm L3 phage display library using the human sIL5R as bait. BmILRbp was localized to the cuticle in *B. malayi* adults and larvae based on confocal imaging and immunoelectron microscopy and shown to be released in the excretory/secretory products. Molecular characterization of BmIL5Rbp revealed no homology to human IL-5, but sequence comparisons revealed that almost all other helminth parasites have BmIL5Rbp orthologues. When expressed in recombinant form, this 19kDa protein was found to bind to the IL5R in the micromolar range by plasmon surface resonance. rBmIL5 was unable to induce STAT-phosphorylation in human eosinophils nor did it prolong eosinophil survival. Rather, it inhibited the ability of human IL-5 to prolong eosinophil survival and phosphorylate Stat-3 and -5. After having shown that BmIL5Rbp is also a murine IL-5 antagonist, we have demonstrated, using a house dust mite (HDM) model of pulmonary type 2 eosinophil-mediated inflammation, that intranasal administration of rBmIL5Rbp dramatically reduced the numbers and frequency (up to 80%) of pulmonary eosinophils following HDM sensitization, a reduction not dissimilar to that induced by a neutralizing anti-IL5 antibody. Moreover, a structural basis for these observations using computational modeling and simulations have been identified; this in advance of considering rBmIL5Rbp (or related molecules) as a parasite-encoded therapeutic for IL-5-mediated disorders.

5) **Transforming growth factor beta (TGFβ) mimic 4 (TGM4) of *Heligmosomoides polygyrus* targets myeloid cells through TGFb receptors and multiple coreceptors.**

SHASHI PRAKASH SINGH[1], KYLE T. CUNNINGHAM[1], MADELEINE P.J. WHITE[1], DANIELLE SMYTH[1,2], SERGIO LILLA[3], SARA ZANIVAN[3], MAARTEN VAN DINTHER[4], PETER TEN DIJKE[4] ANANYA MUKUNDAN[5], ANDREW P. HINCK[5], AND RICK M. MAIZELS[1]

[1]WELLCOME CENTRE FOR INTEGRATIVE PARASITOLOGY, SCHOOL OF INFECTION AND IMMUNITY, UNIVERSITY OF GLASGOW, UK; [2]UNIVERSITY OF DUNDEE, UK; [3]CRUK BEATSON INSTITUTE, SWITCHBACK ROAD, BEARSDEN, GLASGOW G61 1BD, UK; [4]DEPARTMENT OF CELL AND CHEMICAL BIOLOGY, LEIDEN UNIVERSITY MEDICAL CENTER, THE NETHERLANDS; [5]DEPARTMENT OF STRUCTURAL BIOLOGY, UNIVERSITY OF PITTSBURGH, USA.

The murine helminth parasite, *Heligmosomoides polygyrus* secretes a family of ten similar transforming growth factor beta (TGFβ) mimics, named TGM1 to 10, and these proteins contain multiple CCP or Sushi domains. Previously, we have reported that domains 1/2/3 of the 5-domain protein TGM1 are responsible for directly activating host TGFβ receptors I and II, while domains 4/5 interact with the coreceptor CD44. TGM1 induces SMAD signalling, which in turn results in differentiation of CD4+ T helper cells into Foxp3+ T regulatory cells. Currently, the roles of other TGMs are unknown. Here, we report a comparision of TGM1 and TGM4 binding with fibroblasts, T-cells, macrophage cell lines and total spleen cells. In all cell types tested, TGM4 binding is higher compared with TGM1 in flow cytometry, but stimulation of pSMAD2 by TGM4 was observed only in immune cells. Further, we have examined full length and truncated versions (domains 1/2/3 and 4/5) of TGM4 for their interaction with fibroblasts by flow cytometry and GFP-TRAP pull down. We confirm that, like TGM1, domains 1/2/3 of TGM4 associate with TGFβ receptors I and II and domains 4/5 interacts with CD44. Compared to TGM1 the affinity of TGM4 is higher for TGFβ receptor I and CD44, and lower for TGFβ receptor II, however in fibroblasts TGM4 is a poor activator of pSMAD2. The stronger affinity of TGM4 with other cell types suggested involvement of multiple coreceptors binding. Hence, by combining pull down assays from fibroblasts, macrophage cell lines and total spleen cells, we identified novel binding partners specific to TGM4. These co-receptors include Neuropilin1 (CD304), CD49d, and CD72. These data suggest that the parasite targets immune cells for TGFβ signalling through affinity for multiple co-receptors that are absent from fibroblasts and other stromal cells, thereby focussing its effects on populations that are pivotal for worm survival in vivo.

6) **Greedy Worms: manipulating PUFA metabolism to survive and influence host immunity**

ELLA REED, MAZVYDAS KOVECKIS, VALORIE O'DONNELL, MARK YOUNG, **KATHERINE SMITH**

CARDIFF UNIVERSITY, UNITED KINGDOM

The Oxford Languages' definition of parasite is "an organism that lives in or on an organism of another species (its host) and benefits by deriving nutrients at the other's expense". Heavy soil-transmitted helminth (STH) infections of humans are associated with impaired growth and physical development, anaemia and proteinemia, Vitamin A deficiency and poor lactose digestion. In livestock, STH infection reduces productivity, resulting in an estimated loss of €1.8 billion per year in Europe in 2020. Evidence has accumulated that helminth modification of the gastrointestinal microbiota can alter the production of short-chain fatty acids, derived from the metabolism of carbohydrate. These alterations have been shown to result in the regulation of inflammatory conditions in the host and promote STH survival. Our lab has demonstrated that infection with *Heligmosomoides polygyrus bakeri* (Hpb) alters the production of metabolites derived from the essential dietary polyunsaturated fatty acids (PUFA): linoleic acid (omega-6) and alpha-linolenic acid (omega-3) in the colon. Manipulation of cyclooxygenase-derived metabolite production and prostaglandin E_2 receptor signalling implicated PGE_2 as a driver of colorectal cancer development following helminth infection. We also demonstrate that the Hpb genome encodes potential homologues of the enzymes involved in PUFA metabolism and the production of PGE_2, including a protein with 35% amino acid identity to human secretory phospholipase A_2 and a protein with 39% amino acid identity to human prostaglandin E synthase 2. Expression analysis and preliminary *in vitro* assays suggest these homologues play a role in modifying host intestinal cell permeability and in regulating survival of the adult worm. This work highlights an important pathway for controlling helminth persistence, as well as in helminth regulation of host immune responses.

7) *Ascaris suum* extracellular vesicles target human monocytes to generate a unique phenotype affecting T-cell anergy

Anne Borup[1,2], litte S. Rossen[1,2], Bradley Whitehead[1,2], Anders T. Boysen[1,2], Andrea Ridolfi[3,4,5], marco Brucale[3,4], Francesco Valle[3,4], Lucia Paolini[3,6], Paolo Bergese[3,6,7], **Peter Nejsum**[1,2]

[1]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. [2]Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark. [3]Consorzio Interuniversitario per lo Sviluppo dei Sistemi a Grande Interfase (CSGI), University of Florence, Florence, Italy. [4]Consiglio Nazionale delle Ricerche (CNR), Istituto per lo Studio dei Materiali Nanostrutturati (ISMN), University of Bologna, Bologna, Italy. [5]Department of Chemistry, University of Florence, Florence, Italy. [6]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy. [7]Consiglio Nazionale delle Ricerche (CNR), Institute for Research and Biomedical Innovation (IRIB), University of Palermo, Palermo, Italy.

Helminths cause chronic infection in the host through modulation of the host immune response. They suppress the pro-inflammatory type 1 response in favour of a modulated type 2 response by releasing excretory/secretory products (ESPs). Extracellular vesicles (EVs) have been shown to be released with the ESPs; however, their immunomodulatory mechanism is not fully understood. Using flow cytometry, we demonstrate that *Ascaris suum* EVs are selectively internalised in monocytes of human PBMCs. EVs induced phenotypic changes in the monocyte to a unique CD14+, CD16-, CC chemokine receptor 2 (CCR2-) and programmed death-ligand 1 (PD-L1+) expression profile. The downregulation of CD16 expression was partly due to enzymatic activity by metalloproteinases, which did not cause the loss of CCR2 expression. Enzymatic removal of N-linked glycans from the surface of EVs did not alter their effect on the monocytes' expression profile. *Ascaris suum* EVs attenuated T-cell activation, as measured by interferon-γ (IFN-γ), interleukin-10 (IL-10) and IL-2, in a monocyte depended way. Lastly, we demonstrate for the first time that these immunomodulatory effects are mainly caused by EVs and not the EV-depleted fractions. This show that EVs from intestinal helminths can affect circulating immune cells demonstrating that EVs can suppress the immune response.

8) Helminthic glutamate dehydrogenase-dependent PGE_2 production in monocyte and microglia potentiates Treg development with distinct transcriptional profiles

Ulrich F. Prodjinotho[1,7], Vitka Gres[2§], Fiona Henkel[3§], Matthew Lacorcia[1], Ramona Dandl[4], Martin Haslbeck[4], Veronika Schmidt[5,6,7], Andrea S. Winkler[5,6,7], Chummy Sikasunge[8], Per-Johan Jakobsson[9], Philipp Henneke[2,10], Julia Esser-von Bieren[3], **Clarissa Prazeres da Costa[1, 7,11]**

[1]Institute for Medical Microbiology, Immunology and Hygiene, TUM School of Medicine, Technical University of Munich (TUM), Munich, Germany, [2]Institute for Immunodeficiency, Center for Chronic Immunodeficiency, Medical Center and Faculty of Medicine, University of Freiburg, Freiburg, Germany, [3]Center of Allergy and Environment (ZAUM), Technical University of Munich and Helmholtz Center Munich, Munich, Germany, [4]Department of Chemistry, Technical University Munich (TUM), Garching, Germany, [5]Department of Neurology, University Hospital, Klinikum rechts der Isar, Technical University Munich (TUM), Munich, Germany, [6]Center for Global Health, Institute of Health and Society, University of Oslo, Oslo, Norway, [7]Center for Global Health, TUM School of Medicine, Technical University of Munich (TUM), Munich, Germany, [8]School of Veterinary Medicine, Department of Paraclinicals, University of Zambia, Lusaka, Zambia, [9]Rheumatology Unit, Department of Medicine, Solna, Karolinska University Hospital, Stockholm, Sweden, [10]Center for Pediatrics and Adolescent Medicine, Medical Center–University of Freiburg, Freiburg, Germany, [11]German Center for Infection and Research (DZIF), Partner Site Munich, Munich 81675, Germany

[§]These authors contributed equally

Introduction: Immunoregulation of inflammatory, infection-triggered processes in the brain constitutes a central mechanism to control devastating disease manifestations such as epilepsy. In neurocysticercosis (NCC), an inflammatory and clinically pleomorphic disease of the human brain, and most common cause of epilepsy in endemic regions, the disease severity strongly depends on the viability of the larval cyst of the pork tapeworm *T. solium*. Whereas decaying cysts are often associated with epileptic manifestations, viable cysts in the brain mostly remain clinically silent by yet unknown mechanisms, potentially involving regulatory T cells (Tregs) in controlling inflammation.

Objective: In this work, we aim to uncover the underlying mechanisms for this dichotomy, especially the nature of cyst products and mechanisms controlling the development of Tregs during asymptomatic NCC and inflammation during symptomatic NCC.

Materials and Methods: Peripheral and brain immune cells from mice and healthy volunteers were pulsed with parasite viable, decaying cyst materials and the recombinant expressed cyst enzyme glutamate dehydrogenase GDH. Immune modulation and underlying mechanistic aspects were identified via adoptive transfer of cyst-treated DCs, and qPCR/FACS surrogate markers expression associated with LC/MS/MS profiling of eicosanoids and precursors and PGE2/IL-10 receptors antagonists. The mechanisms underlying Treg development such as transcriptional

signatures associated with GDH-PGE2/IL-10-induced Tregs were furthermore assessed in sorted Tregs from Tanzanian NCC patients.

Results: We demonstrated that the enzyme GDH from parasite viable cyst instructs tolerogenic $CD206^{+}$ monocytes and $Iba\text{-}1^{lo}$ microglia to release IL-10 and the lipid mediator PGE_2. These act in concert via their respective receptors, converting naive $CD4^{+}$ T cells into brain homing $CD25^{hi}FoxP3^{+}CTLA\text{-}4^{+}CCR6^{+}CCR7^{+}$ Tregs with distinct transcriptional signatures (e.g. JAK-STAT pathway) as identified in asymptomatic NCC patients. Moreover, while viable cyst strongly upregulated IL-10 and PGE_2 transcription in microglia leading to Treg development, dead cyst material lacking GDH enzyme induced proinflammatory non-phagocytic microglia and TGF-β as potential drivers of epilepsy.

Conclusion: Harnessing the GDH-PGE_2-IL-10 axis and targeting TGF-ß signaling may offer an important therapeutic strategy in inflammatory epilepsy and NCC.

9) **Schistosomal extracellular vesicle-enclosed long non-coding RNAs are transferred to the mammalian host**

RAQUEL SILVEIRA DE OLIVEIRA1, ANA CAROLINA TAHIRA1, PABLO Q. F. DA MOTTA1, THAIS L. DA SILVA1, SERGIO VERJOVSKI-ALMEIDA1,2, TAL MENINGHER3, DROR AVNI3,4, **MURILO S. AMARAL 1**

1LABORATÓRIO DE CICLO CELULAR, INSTITUTO BUTANTAN, SAO PAULO, BRAZIL 2DEPARTAMENTO DE BIOQUÍMICA, INSTITUTO DE QUÍMICA, USP, SAO PAULO, SP, BRAZIL
3 LABORATORY OF MOLECULAR CELL BIOLOGY, SHEBA MEDICAL CENTER, TEL HASHOMER, ISRAEL
4SACKLER FACULTY OF MEDICINE, TEL-AVIV UNIVERSITY, ISRAEL

Schistosoma mansoni is a trematode that causes schistosomiasis, a neglected tropical disease that affects more than 200 million people worldwide. Adult parasites can live for decades inside the mesenteric veins of infected humans, as the result of a complex parasite-host communication system that includes the release of parasite extracellular vesicles (EVs). EVs are cell derived membrane-enclosed particles that vary by their size, content, and intra-cellular origin. It was demonstrated that *S. mansoni* worms secrete EVs, however their bioactive cargo, function, and selective targeting are poorly understood. Long non-coding RNAs (lncRNAs) are RNAs longer than 200 nucleotides with low or no protein-coding potential that have been explored as new therapeutical targets in human diseases. We have recently shown that the knockdown of *S. mansoni* lncRNAs affects the pairing status of these parasites, showing potential as therapeutic targets. Here, we show for the first time that EVs released by *S. mansoni* harbor lncRNAs. We have performed RNA-Seq of EVs released in vitro by adult *S. mansoni* worms and identified thousands of lncRNAs (SmEV-lncRNAs) inside the EVs. Selected SmEV-lncRNAs were validated by RT-qPCR in independent SmEV samples. Remarkably, we found by RNA-Seq that most of the SmEV-lncRNAs were also found in the mesenteric lymph nodes or Peyer's patches of infected hamsters but not in non-infected ones, indicating in vivo SmEV-lncRNA transfer to the mammalian host. On the other hand, SmEV-lncRNAs were not detected in the serum of infected hamsters, indicating low abundance or a fast lncRNA/EV turnover. These results add another layer to the understanding of parasite-host communication, in which SmEV-lncRNAs may participate in modulation of the host immune system. In addition, this worm-host crosstalk mechanism can be explored in the development of new diagnostic and therapeutic approaches against schistosomiasis.

10) **RNA communication in helminth-host interactions**

Amy H Buck[1], Kyriaki Neophytou[1], Ruby White[1], Roberto Bermudez Barrientos[1], Elaine Robertson[1], Tom Youdale[1], Tom Fenton[1], Frances Blow[1], Cei-Abreu-Goodger[2]

1 Institute of Immunology & Infection Research
2 Institute of Ecology & Evolution
Ashworth Labs, King's Buildings, School of Biological Sciences, University of Edinburgh

Cross-species communication is required for proper functioning of the mammalian gut, where different organisms share resources, coordinate digestion and maintain homeostasis. In many animals, parasitic worms (helminths) are part of this ecosystem, where they communicate through the release of bio-active molecules that promote immunological tolerance and modulate gut functions. We discovered that the gastrointestinal nematode Heligmosomoides bakeri releases extracellular vesicles that are internalized by mouse cells and suppress type 2 immune responses. The extracellular vesicles contain at least three classes of small RNAs and we have identified a parasite-derived Argonaute protein "exWAGO" that specifically binds to secondary siRNAs within the extracellular vesicles, and appears to be involved in their selective export and import into host cells. Many of the exWAGO-bound siRNAs derive from transposable elements in the parasite genome and our current work is focused on understanding how these regulate gene expression in mammalian (host) epithelial cells. In parallel we have developed methods to detect parasite proteins and RNAs present in the extracellular vesicles which we are currently using to visualize uptake by target cells during the natural infection, suggesting distinct tropism of extracellular vesicles over the life stage of the parasite. Collectively our data suggest that nematode parasites have evolved specific factors to enable selective and specific RNA transmission to mouse cells and work is ongoing to define the host pathways that are regulated by this cross-species RNA interference pathway during the infection.