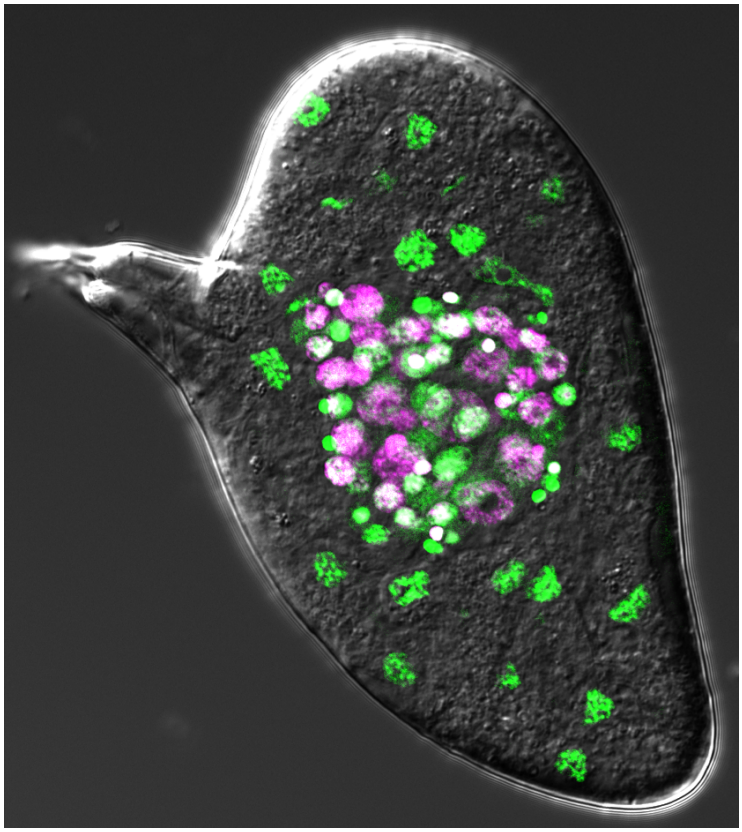
Molecular and Cellular Biology of Helminths XII



2 - 7 September 2018
Bratsera Hotel, Hydra, Greece

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PLOS | NEGLECTED TROPICAL DISEASES

MOLECULAR AND CELLULAR BIOLOGY OF HELMINTH PARASITES

I. **6-9 September 1997, Edinburgh, UK**
'Parasitic Helminths from Genomes to Vaccines'

II. **8-11 July 1999, Edinburgh, UK**
'Parasitic Helminths from Genomes to Vaccines II'

III. **14-19 September 2002, Hydra, Greece**
'Molecular and Cellular Biology of Helminth Parasites III'
Special Issue of *International Journal of Parasitology* **33 (11):** 1127-1302

IV. **6-11 September 2005, Hydra, Greece**
'Molecular and Cellular Biology of Helminth Parasites IV'
Special Issue of *International Journal of Parasitology* **36 (6):** 615-733

V. **12-17 September 2008, Hydra, Greece**
'Molecular and Cellular Biology of Helminth Parasites V'

VI. **5-10 September 2010, Hydra, Greece**
'Molecular and Cellular Biology of Helminth Parasites VI'
Special Issue of *Experimental Parasitology* **132** (1) : 1-102

VII **2-7 September 2012, Hydra, Greece**
'Molecular and Cellular Biology of Helminth Parasites VII'

VIII **1-6 September 2014, Hydra Greece**
'Molecular and Cellular Biology of Helminth Parasites VIII'

IX **31 August – 5 September 2015, Hydra Greece**
'Molecular and Cellular Biology of Helminth Parasites IX'

X **4 – 9 September 2016, Hydra Greece**
'Molecular and Cellular Biology of Helminth Parasites X'

XI **3-8 September 2017, Hydra Greece**
'Molecular and Cellular Biology of Helminth Parasites XI'

Dates of MCBHP-XIII Meeting: 1-6 September 2019

ORGANISERS, 2018
Richard E Davis (University of Colorado, School of Medicine, USA)
Kleoniki Gounaris (Imperial College, UK)
Rick Maizels (University of Glasgow, UK)
Murray Selkirk (Imperial College, UK)

Cover photo : Developing *Schistosoma mansoni* embryo. Nuclei in green, proliferative nuclei labeled in magenta. Credit: Jipeng Wang, laboratory of Dr James Collins, University of Texas Southwestern Medical Center

	Sunday 2 September	Monday 3 September	Tuesday 4 September	Wednesday 5 September	Thursday 6 September	Friday 7 September
	ARRIVE	**Session 1 Parasite Effectors**	**Session 4 Host Immunity 2**	**Session 7 Regulation of Inflammation**	**Session 10 Schistosome Biology**	DEPART
09:00		**Thomas Baum**	De'Broski Herbert	Frank Brombacher	**Tim Anderson**	
09:20			Catherine Sharpe	Marta de los Reyes		
09:40		David Bird	Si Wang	Justin Nono	Christoph Grevelding	
10:00		Sutas Suttiprapa	Tomáš Macháček	Stephanie Ryan	Min Hu	
10:20		Andrew Hinck	Marion Rolot	William Harnett	Roman Leontovyč	
10:40-11:10			**Coffee break**			
		Session 2 Host Immunity 1	**Session 5 Development & Host Interactions**	**Session 8 Drugs and Anthelmintics**	**Session 11 Coinfection & Systemic Impacts**	
11:10		**Andrea Graham**	**Jim Collins**	Phil LoVerde	**Alison Elliott**	
11:30				Simone Haeberlein		
11:50		Jesuthas Ajendra	Klaus Brehm	Paul Selzer	Hendrik van der Zande	
12:10		William Horsnell	Maria Duque-Correa	Mark Wilson	Benjamin Dewals	
12:30		Deirdre Joy / NIH	Bonnie Douglas	Murray Selkirk	Katherine Smith	
12:50-4:30			**Afternoon break**			
		Session 3 Genomics	**Session 6 Developmental Biology & Life History**	**Session 9 Small RNAs**	**Session 12 Vaccination**	
4:30	**Registration Opens at Bratsera Hotel**	Dick Davis	**Celine Cosseau**	**Julie Claycomb**	Sara Lustigman	
4:50		Jianbin Wang			Jimmy Borloo	
5:10		Faye Rodgers	Patrick Driguez	Collette Britton	Eve Hanks	
5:30		**Poster Pitches, 11 x 2 minutes**	Adrian Streit	**Poster Pitches 11 x 2 minutes**	Mark Pearson	
5:50			*End of Session*		Rick Maizels	
6:45	**Pre-lecture drinks**	**Poster Session 1**	**Vlychos Taverna Dinner (Boat leaves 7:00 PM)**	**Poster Session 2**	*End of Session*	
7:45	**Keynote Lecture: Graham LeGros**				**Bratsera Farewell Dinner (8:30 PM)**	
9:00	**Welcome Reception**	*End of Session*		*End of Session*		

NOTES

Sunday 2 September

Chair: **Rick Maizels**, University of Glasgow	
19:45	**Keynote Lecture:** **Graham LeGros, Malaghan Institute for Medical Research, Wellington, NZ** **Learning to love our parasites: The exquisite and sometimes beneficial relationship between parasitic nematodes and the mammalian immune system**
21:00	**Welcome Reception and Dinner, Bratsera Hotel**

Monday 3 September

09:00 - 10:40 Session 1: Parasite Effectors

Chair: **Murray Selkirk**, Imperial College London		
09:00	**Thomas Baum,** Iowa State University, USA	**Genome and effector biology of the soybean cyst nematode**
09:40	**David Bird,** North Carolina State University, USA	**A comprehensive model of feeding site formation by root-knot nematodes**
10:00	**Suttas Suttiprapa,** Khon Kaen University, Thailand	**Characterization and diagnostic potential of a novel mucinase of the carcinogenic liver fluke *Opisthorchis viverrini***
10:20	**Andrew Hinck,** University of Pittsbugh, USA	**Structure-function studies of the *H. polygyrus* TGF-β mimic TGM**

11:10 – 12:50 Session 2: Host Immunity I

Chair: **De'Broski Herbert**, University of Pennsylvania		
11:10	**Andrea Graham,** Princeton University, USA	**Environmental impacts on host susceptibility in mesocosms for This Wormy World**
11:50	**Jesuthas Ajendra,** University of Manchester, UK	**A study of *Fasciola hepatica* virulence and invasion using omics tools**
12:10	**William Horsnell,** University of Cape Town, South Africa	**Molecular analysis of genes induced by blood feeding in *N. brasiliensis***
12:30	**Deirdre Joy**, National Institutes of Health, USA	**Special Presentation :** **Funding opportunities for helminth research**

16:30 - 18:00 Session 3: Genomics

Chair: **Collette Britton**, University of Glasgow		
16:30	**Jianbin Wang,** University of Colorado, USA	**Programmed DNA elimination in nematodes**
16:50	**Richard Davis,** University of Colorado, USA	
17:10	**Faye Rodgers,** Wellcome Sanger Institute, UK	**Curation of whipworm genomes by WormBase and the community**
17:30	**Pitches for Poster Session 1**	

Monday 3 September - 17:30-18:00 (2 min poster presentations, 2 slides each)

Chair: **Niki Gounaris,** Imperial College London			
1	**Nada Abdel Aziz**	ICGEB, Cape Town, South Africa	Foxp3^{+} regulatory T cells require IL-4Rα signaling to control helminth-induced lung emphysema
2	**Nichola Calvani**	Sydney School of Veterinary Science, Australia	A flexible molecular diagnostic method for the diagnosis of *Fasciola* spp. in ruminant faecal samples
3	**Anja de Lange**	University of Cape Town, South Africa	Investigating the presence and activity of acetylcholinesterases in *Taenia crassiceps* larvae and their excretory/secretory products, and the ability of these to functionally effect neuronal electrophysiology
4	**Samantha Del Borrello**	University of Toronto, Canada	Using simulated hypoxia in *C. elegans* as a platform for anthelmintic drug discovery
5	**Colette Dissous**	Institut Pasteur de Lille, France	Venus Kinase Receptors in the flatworm *Macrostomum lignano*
6	**Santiago Fontenla**	Universidad de la Republica, Uruguay	Evolutionary and structural divergence of genes involved in the small RNA pathways of platyhelminthes
7	**Gisela Franchini**	Universidad de la Plata, Argentina	Fatty acid binding proteins (FABP) of parasitic cestodes: functional studies and evaluation as novel therapeutic targets
8	**Nahili Giorello**	Universidad de la Plata, Argentina	Characterization of the major pseudocoelomic proteins of the giant kidney worm, *Dioctophyme renale*
9	**Kevin Howe**	European Bioinformatics Institute, UK	WormBase ParaSite - 2018 update
10	**Brittany-Amber Jacobs**	University of Cape Town, South Africa	Cancer cell behaviour following parasite exposure
11	**Brunette Katsandegwaza**	University of Cape Town, South Africa	Helminths and colitis: friends or foes?

18:30-20:30 Poster Session 1 and Drinks, Bratsera Hotel Courtyard

Tuesday 4 September

09:00 - 10:40 Session 4: Host Immunity -2

Chair: **William Horsnell**, University of Cape Town		
09:00	**De'Broski Herbert** University of Pennsylvania, USA	**IL-33 deficiency in myeloid APC accelerates helminth-induced Type 2 immunity through impairment of intestinal Treg expansion**
09:20	**Catherine Sharpe**, University of Manchester, UK	**Defining the mechanisms of mucosal defence during chronic *Trichuris muris* infection**
09:40	**Si Wang**, China Agricultural University	**Transcriptional profiling reveals a PRRs mediated recognition of *Haemonchus contortus* in sheep**
10:00	**Tomáš Macháček,** Charles University, Faculty of Science, Czechia	**Dynamics of immune cells in the CNS of mice infected by *Trichobilharzia regenti* (Schistosomatidae): implications for parasite clearance**
10:20	**Marion Rolot**, Liege University, Belgium	***Lyz2*-specific deletion of IL-4Rα chain in schistosomiasis does not preclude Ly6C^{high} monocytes as the main source of liver macrophages but impairs alternative activation and increaseσ inflammation**

11:10 – 12:50 Session 5: Development and Host Interactions

Chair: **Adrian Streit**, Max Planck Institue for Developmental Biology		
11:10	**Jim Collins,** University of Texas South Western Medical Center, USA	**Molecular analyses of schistosome reproductive development**
11:50	**Klaus Brehm,** University of Wuerzburg, Gemany	**Genetic and pharmacological analyses into *Echinococcus multilocularis* stem cells and body axes**
12:10	**Maria Duque-Correa,** Wellcome Sanger Institute, UK	**Unravelling early host intestinal epithelia interactions with whipworms using intestinal organoids**
12:30	**Bonnie Douglas,** University of Pennsylvania, USA	**Establishment of a novel transgenesis approach to track helminth-specific CD4^{+} T cells using a 2W1S-expressing model of gastrointestinal nematode infection**

16:30 – 17:50 Session 6: Developmental Biology and Life History

Chair: **Christoph Grevelding**, University of Giessen		
16:30	**Celine Cosseau,** University of Perpignan, France	**Epigenetic Inheritance in *Schistosoma mansoni* – *Biomphalaria glabrata* interactions**
17:10	**Patrick Driguez**, Wellcome Sanger Institute, UK	**Studying the translatome of *Schistosoma mansoni* using ribosome profiling**
17:30	**Adrian Streit,** Max Planck Institute for Developmental Biology, Germany	**Absence of meiotic recombination in the sex chromatin of the nematode *Strongyloides papillosus*.**

Wednesday 5 September

09:00 - 10:40 Session 7: Regulation of Inflammation

Chair: **Niki Gounaris,** Imperial College London		
09:00	**Frank Brombacher,** University of Cape Town, South Africa	**Partial removal of IL-4 receptor alpha within the FoxP3$^+$ regulatory T cell population impairs the control of inflammation in disease**
09:20	**Marta de los Reyes,** Technical University of Munich, Germany	**An immunomodulatory parasite limits type 2 inflammation by reprogramming the arachidonic acid metabolism in myeloid cells**
09:40	**Justin Nono,** University of Cape Town, South Africa	**IL-4 receptor targeting to treat liver fibrosis: Evidence from chronic schistosomiasis in humans, mice and non-human primates**
10:00	**Stephanie Ryan,** James Cook University, Australia	**High-throughput expression of the hookworm recombinant secretome for an *in vivo* screen to find novel therapeutics to treat Inflammatory Bowel Disease**
10:20	**William Harnett,** University of Strathclyde, UK	**Is the *Acanthocheilonema viteae*-derived immunomodulator ES-62 an elixir of life for the male of the species?**

11:10- 12:50 Session 8: Drugs and Anthelminthics

Chair: **Sara Lustigman**, New York Blood Center		
11:10	**Phil LoVerde,** University of Texas Health Science Center, USA	**An iterative approach to the development of novel therapeutics against human schistosomiasis**
11:30	**Simone Haeberlein, J**ustus-Liebig-University, Giessen, Germany	**Insect biotechnology meets schistosomes – the lethal effect of ladybird-derived harmonine on *Schistosoma mansoni***
11:50	**Paul Selzer,** Boehringer-Ingelheim Vetmedica GmbH, Germany	**Identification and profiling of anthelmintic compounds in veterinary parasitology**
12:10	**Mark Wilson,** Genentech, USA	**Epithelial cell-derived phospholipase A_2 group 1B (PLA_2g1B) is an endogenous anthelmintic**
12:30	**Murray Selkirk**, Imperial College, UK	**Nematode secreted cholinesterases and cholinergic regulation of immunity**

16:30 – 18:00 Session 9: Small RNAs

Chair: **Dick Davis**, University of Colorado		
16:30	**Julie Claycomb,** University of Toronto, Canada	**Agonomics: a systematic analysis of Argonaute P proteins and small RNA pathways in *C. elegans***
17:10	**Collette Britton**, University of Glasgow, UK	**Nematode microRNAs – roles in development and host-parasite interactions**
17:30	**Pitches for Poster Session 2**	

Wednesday 5 September

17:30-18:00 **(2 min poster presentations, 1 slide each)**

Chair: **Niki Gounaris,** Imperial College London			
12	**Adrian Leontovyč**	Czech Academy of Sciences	Cathepsins L3 from parasitic flukes as therapeutic targets
13	**Xianyong LIu**	China Agriculatural University	*Haemonchus contortus* soluble extracts suppress NLRP3 inflammasome activation via the circRNA-miRNAs-mRNA axis
14	**Simone Niciura**	Embrapa Pecuaria Sudeste, Brazil	Preliminary genomic analyses of a Brazillian isolate of *Haemonchus contortus* in a model for monepantel resistance
15	**Cassan Pulaski**	Louisiana State University, USA	Clinical validation of molecular markers of macrocyclic lactone resistance in *Dirofilaria immitis*
16	**Anna Rabes**	University Medical Center, Rostock, Germany	Host defense versus immunosuppression: Unisexual infection with male or female *Schistosoma mansoni* differentially impacts the immune response against invading cercariae
17	**Christian Schwartz**	Trinity College Dublin, Ireland	PD-L1-expressing group 2 innate lymphoid cells checkpoint Th2 cells during helminth infection
18	**Martina Sombetzki**	University Medical Center, Rostock, Germany	Single-sex infection with female *Schistosoma mansoni* cercariae mitigates hepatic fibrosis after secondary infection
19	**Nathalie Thuma**	University Hospital Erlangen, Germany	Antigen specificity of the adaptive immune response against *Nippostrongylus brasiliensis*
20	**Chunqun Wang**	Huzahong Agricultural University, China	A comprehensive study of N-glycosylation of *Haemonchus contortus*
21	**Xing-Quan Zhu**	Chinese Academy of Agricultural Sciences	Recombinant *Fasciola gigantica* Ras-related protein Rab-10-like protein modulates various functions of goat peripheral blood mononuclear cells (PBMCs) in vitro

Thursday 6 September

09:00 - 10:40 Session 10: Schistosome Biology

Chair: **Phil LoVerde**, University of Texas Health Science Center		
09:00	**Tim Anderson,** Texas Biomedical Research Institute, San Antonio, USA	**Genetic analysis of biomedically important traits in Schistosomes**
09:40	**Christoph Grevelding,** **J**ustus-Liebig-University, Giessen, Germany	**Kinases and GPCRs of *Schistosoma mansoni*, a subtranscriptomics-based overview about their potential functions for schistosome biology with implications for basic and applied research**
10:00	**Min Hu**, Huazhong Agricultural University, China	**Serine/threonine protein phosphatase 1 (PP1) controls growth and reproduction in *Schistosoma japonicum***
10:20	**Roman Leontovyč,** Charles University, Prague, Czechia	**Comparative transcriptomic analysis shows molecular mechanisms used by visceral and neurotropic avian schistosomes**

11:10 – 12:50 Session 11: Coinfection and Sytemic Impacts

Chair: **Klaus Brehm,** University of Würzburg		
11:10	**Alison Elliott,** MRC/Uganda Virus Research Institute	**Population differences in vaccine responses: do parasitic infections contribute?**
11:50	**Hendrik van der Zande,** **L**eiden University Medical Center, The Netherlands	**The *Schistosoma mansoni* glycoprotein omega-1 improves whole-body metabolic homeostasis independent of its Th2 polarizing capacity**
12:10	**Benjamin Dewals,** Liege University, Belgium	**Helminth-induced IL-4 expands bystander memory CD8$^+$ T cells for early control of viral infection**
12:30	**Katherine Smith,** University of Cape Town, South Africa	**A new risk factor for cancer – how helminth exposure influences colorectal cancer development.**

16:30 – 18:10 Session 12: Vaccination

Chair: **Mark Wilson**, Genentech		
16:30	**Sara Lustigman,** New York Blood Center, USA	**Developing of a prophylactic vaccine to accelerate onchocerciasis elimination**
16:30	**Jimmy Borloo**, Ghent University, Belgium	**Structural and immunological approach to ASP-based vaccine development against cattle parasites *Ostertagia ostertagi* and *Cooperia oncophora***
17:10	**Eve Hanks,** University of Glasgow, UK	**Determining anti-glycan antibody responses to *Haemonchus contortus* Barbervax vaccine using glycan microarray screening**
17:30	**Mark Pearson,** James Cook University, Australia	**Profiling the human antibody response to *Schistosoma haematobium* infection by probing protein microarrays with urine and sera from infected individuals**
17:50	**Rick Maizels**, University of Glasgow, UK	**Extracellular vesicle vaccines for immunity to helminths**

20:30	**Farewell Banquet, Bratsera Hotel**

ABSTRACTS

KEYNOTE LECTURE

Learning to love our parasites: The exquisite and sometimes beneficial relationship between parasitic nematodes and the mammalian immune system

GRAHAM LEGROS

MALAGHAN INSTITUTE OF MEDICAL RESEARCH, WELLINGTON, NEW ZEALAND

Using the immunological and metabolic impact of a parasite on its natural host to change health outcomes is an area of rejuvenated scientific investigation. This is driven in part by the almost paradoxical emergence of many chronic inflammatory and metabolic conditions in human populations that transition from environments where chronic infection with multiple species of parasite throughout life is the norm to a situation where people are never exposed to parasites. We have used our improved experimental techniques for measuring, monitoring and manipulating the immune system to bring renewed focus on how parasites have evolved to manipulate the mammalian immune system. The recent gene cloning of immune regulatory molecules from the rodent parasite *Heligmosomoides polygyrus* has opened up potential new opportunities in critical areas of human health. The observation that a gut dwelling parasite can so precisely target distinct parts of the mammalian immune system not only making things more comfortable for itself but also potentially impacting on the way its host responds to other infectious microbes and antigenic challenges at other sites in the body is important. We used the same *H. polygyrus* model to explore in more detail how chronic gut parasite infection influences the susceptibility to developing allergic skin reactions to common human allergens, and influences susceptibility to infections by other species of nematode parasites.

As predicted from previous studies, *H. polygyrus* infection greatly reduced the severity and duration of allergic immune responses in the skin of mice when exposed to common allergens. However, when the same mouse host was challenged by infection with a tissue migrating nematode such as *Nippostrongylus brasiliensis* it was found to be not immune-compromised but instead able to mount striking immune-mediated killing responses against tissue migrating *N. brasiliensis* larvae. Significantly, the host mice also had reduced lung pathology associated with this tissue migratory parasite. How the *H. polygyrus* infected mouse is able to mount what seem to be bipolar responses depending on the antigenic challenge suggests that at least some species of parasitic worms can induce in the gut of their host quite complex and mutually beneficial immunological relationships. We are currently focused on trying to translate these findings to improving the human condition using the human hookworm *Necator americanus*. The scientific challenge of producing highly defined N. americanus larvae for use in human therapy while significant is not impossible given the cutting-edge laboratory techniques that have been developed for less highly specialized but related nematodes such as *C. elegans*.

Genome and Effector Biology of the Soybean Cyst Nematode

THOMAS J. BAUM

DEPT OF PLANT PATHOLOGY AND MICROBIOLOGY; IOWA STATE UNIVERSITY, AMES, IOWA, USA

Unlike migratory plant-parasitic nematodes, which feed continuously from their host plants, the soybean cyst nematode (*Heterodera glycines*), like all cyst nematodes, only feeds during a sedentary life period deep inside the plant tissue. Extended feeding in one location became possible because these nematodes have evolved the ability to manipulate the developmental fate and physiology of host plant cells that fuse to form specialized feeding organs in response to the nematode's manipulations. Furthermore, cyst nematodes effectively suppress numerous plant defense responses. Many of these feats are accomplished through nematode protein secretions, so-called effectors that are delivered into the plant tissue. It is important to gain an understanding of the nematode's adaptions for parasitism that enable these intricate host-parasite interactions. In support of this goal, high-quality genome assemblies along with transcriptomic and genomic sequences of many *H. glycines* strains are now available. The genes underpinning cyst nematode parasitism and virulence are increasingly available and their molecular characterization has revealed key insights into their function. This presentation will provide selected highlights portraying the status of *Heterodera* genomics and our understanding of the molecular plant-cyst nematode interactions.

A comprehensive model of feeding site formation by root-knot nematodes.

DAVID BIRD

NORTH CAROLINA STATE UNIVERSITY, RALEIGH, NORTH CAROLINA, USA

Those species of plant-parasitic nematode that cause the most agricultural/economic damage irrevocably commit to a sedentary life style within the host. The parasite remains dependent on a feeding site that forms in the root vasculature. For root-knot nematode (RKN: *Meloidogyne* spp.), the feeding site is a characteristic cluster of giant cells (GC). In general, all vascular plants are susceptible to this developmental manipulation by nematodes, and models of function must accommodate this broad host range. GC induction is a digital event, likely orchestrated by the plant hormone, cytokinin. RKN produce and secrete this plant hormone, likely throwing a developmental switch. To understand the events that follow, we developed genetic resources for M. hapla, including the ability to map nematode loci that influence expression of plant genes. Genetic data are directional, and point to causality. One locus on Linkage Group 4, which we named HEM (Host Expression Modulator), is highly pleiotropic, influencing expression of more than 60 plant genes. Based on mapping the recombination breakpoints flanking HEM, this locus has been localized to 87KB. The function of the HEM genes remains obscure. Another region of interest, defined by a broad QTL for nematode fecundity, spans a cluster of genes predicted to encode mimics of secreted plant peptide hormones, which we termed xenomones. Plants have hundreds of transmembrane receptors to monitor the environment. Using NMR, we solved the structure of several xenomones, and used Molecular Dynamics Simulation to explore xenomone-receptor binding. Intriguingly, some of the ligands proved to be promiscuous, and point to a mechanism by which cytokinin-stimulated stem cells, deprived of external stimuli from their now incapacitated receptors might develop into GC. Although, the true plant ligands likely function in the nanomolar range, structural diversity in the nematode arsenal of xenomones likely suffices to span the receptor space.

Characterization and diagnostic potential of a novel mucinase of the carcinogenic liver fluke *Opisthorchis viverrini*

RIEOFARNG DONTUMPRAI[1], ISABELLE JALA[2], SIRIKANYA PLUMWORASAWAT[1], MANOP SRIPA[2], BANCHOB SRIPA[3], **SUTAS SUTTIPRAPA**[2]

[1]DEPARTMENT OF MICROBIOLOGY, FACULTY OF SCIENCE, MAHIDOL UNVERSITY, BANGKOK 10400, THAILAND, [2] TROPICAL MEDICINE GRADUATE PROGRAM (INTERNATIONAL PROGRAM), TROPICAL DISEASE RESEARCH CENTER, [3]DEPARTMENT OF PATHOLOGY, FACULTY OF MEDICINE, KHON KAEN UNIVERSITY, KHON KAEN 40002, THAILAND

The liver fluke *Opisthorchis viverrini* is endemic in Thailand, Lao PDR, Vietnam and Cambodia. The infection in humans causes hepatobiliary abnormalities including bile duct cancer–cholangiocarcinoma (CCA) cancer. Goblet cell metaplasia and mucus gland hyperplasia are commonly found in the *O. viverrini* infected bile duct. These indicate the increased mucin production in response to the invading parasite. To survive in the bile duct filled with mucin, *O. viverrini* must contain mucinase enzyme or other mechanism to destroy and remove the mucin barrier. This study aimed to investigate the mucinase activity of this liver fluke. The experiment was conducted by adding bovine submaxillary mucin (BSM) into culture medium of *O. viverrini* adult worm. Western blot analysis revealed that *O. viverrini* was able to digest the mucin and mucinase activity was partially inhibited by EDTA. A putative mucinase enzyme was identified from proteome and transcriptome of *O. viverrini.* Sequence analysis, cloning and expression of recombinant protein were performed. The putative mucinase contains a conserved zinc-dependent metallopeptidase HEXXH motif. Recombinant protein was expressed in *Escherichia coli*. Substrate specificity and enzyme kinetics are being investigated. Given the low sequence similarity (<25%) to other proteins on the public database, this novel mucinase is a potential diagnostic marker for *O. viverrini* infection. Indeed, western blot analysis revealed that the protein reacted to the serum from *O. viverrini* infected patients. The sensitivity and specificity of this novel diagnostic antigen will be further investigated.

Structure-function studies of the *H. polygyrus* TGF-β mimic TGM

ANANYA MUKUNDAN[1], CHANG-HYEOCK BYEON[1], CYNTHIA S. HINCK[1], DANIELLE SMYTHE[2], RICK MAIZELS[2], **ANDREW P. HINCK**[1]

[1]DEPARTMENT OF STRUCTURAL BIOLOGY, UNIVERSITY OF PITTSBUGH SCHOOL OF MEDICINE, PITTSBURGH, PA USA; [2]WELLCOME CENTRE FOR MOLECULAR PARASITOLOGY, INSTITUTE OF INFECTION, IMMUNITY AND INFLAMMATION, UNIVERSITY OF GLASGOW, U.K.

The mouse parasite *Heligmosomoides polygyrus* evades host immune responses by secreting a protein known as HpTGM that binds directly to the TGF-β receptors. This activates the TGF-β pathway and dramatically increases the population of immunosuppressive Fox3p^{+} T_{regs}. HpTGM, which is comprised of five homologous domains (D1-D5), each with approximately 90 amino acids and two characteristic disulfides, belongs to the complement control protein (CCP) family. The CCP family has no homology to the TGF-β family and thus HpTGM is a structurally distinct evolved TGF-β mimic. To better understand how *Hp*TGM recognizes and assembles TβRI and TβRII into a signaling complex, binding studies with the different domains of HpTGM and the TGF-β receptors were performed using NMR and ITC and correlated with results from cell-based TGF-β reporter assays. These showed that TGM D1 and D2 cooperate to bind TβRI with the same high affinity as full-length HpTGM, while TGM D3 alone binds TβRII. Through NMR-based structural analysis, TGM-D3 was shown to adopt the same four-stranded antiparallel β-sheet characteristic of CCP family proteins, but differs in that it formed a continuous half β-barrel rather than two unconnected antiparallel β–strands. Through NMR, we further showed that TβRII uses the same exposed β-strand to bind TGM-D3 NMR as it does to bind TGF-βs, consistent with TGM-D3 competing against TGF-β for binding to TβRII. TGM D1-D2 did not compete against TGF-β in luciferase reporter assays, indicating that TβRI appears to use a different surface to contact TGM D1-D2 and TGF-β. The emerging picture from these studies is that TGM appears to mimic TGF-β in two important ways - first by binding TβRI and TβRII in close spatial proximity - second by binding TβRII through a single chain, but by binding and gaining very high affinity for TβRI by contacting it through multiple chains.

Environmental impacts on host susceptibility in mesocosms for This Wormy World

ANDREA GRAHAM

PRINCETON UNIVERSITY, PRINCETON, NEW JERSEY, USA

Why do hosts vary in how vigorously, and how effectively, they combat parasites? Reciprocally, why do parasites vary so much in their growth and survival within hosts? Genotype and environment are each likely to impact the answers to such questions. We have begun studies of colonic nematodes in mice of selected genotypes under semi-natural environmental variation, in experimental mesocosms. Our initial findings reveal strong effects of environment: While C57BL/6 mice are resistant to high doses of *Trichuris muris* eggs under laboratory conditions, mice released outdoors for just 2 weeks harbored greatly increased worm burdens and worm biomass. We discovered enhanced microbial diversity and specific bacterial taxa predictive of nematode burden in outdoor mice. We also observed decreased type 2 immune responses in lamina propria and mesenteric lymph node cells from infected mice outdoors. These results demonstrate that environment can rapidly and significantly shape gut microbial communities and mucosal responses to gastrointestinal nematode infections. We are now further developing this mesocosm system to better characterize behavioral and nutritional mechanisms by which hosts in natural populations may compensate for costs of parasitism and defense. This system provides a unique bridge between controlled laboratory immunoparasitology and host-parasite interactions in nature.

IL-17 and neutrophils in the development of a type 2 immune response during helminth infection

JESUTHAS AJENDRA, ALISTAIR CHENERY, BRIAN CHAN, JAMES PARKINSON, STELLA PEARSON, TARA E. SUTHERLAND, JUDITH E. ALLEN

FACULTY OF BIOLOGY, MEDICINE AND HEALTH, WELLCOME CENTRE FOR CELL-MATRIX RESEARCH, UNIVERSITY OF MANCHESTER, UK

Immune responses during helminth infections are typically type 2 responses, mainly characterized by the induction of type 2 cytokines such as IL-4, IL-5 and IL-13 and eosinophilia. However, the early phase of infection with the lung-migrating nematode *Nippostrongylus brasiliensis* (Nb) is dominated by innate IL-17 production and neutrophilia. In this project, we are investigating the importance of this early IL-17 and neutrophilia in the development of a type 2 immune response. Mice deficient in IL-17A failed to recruit neutrophils and subsequently did not mount a full type 2 immune response against Nb leading to an increased worm burden. Neutrophil depletion in WT mice during the early stages of infection with Nb lead to impaired lung eosinophilia and decreased IL-4+ CD4+ T cell numbers. However, neutrophil-depleted mice were equally as able to expel their parasites as isotype-treated controls. In addition, transfer of neutrophils into IL-17A-/- mice did not fully rescue the impaired type 2 immune response. A striking observation was that IL-17A-deficient mice exhibited increased IFNγ production in the lung by T cells, NK1.1+ cells and γδ T cells during the early phase of Nb infection. Our data suggest that IL-17A promotes type 2 responses by suppressing IFNγ and thereby setting an ideal milieu for a type 2 response to develop.

Pre-conception maternal helminth infection transfers via nursing long lasting cellular immunity against helminths to offspring

MATTHEW DARBY[1], BENJAMIN DEWALS[2], DUNJA MRJDEN[1], CLAIRE MACKOWIAK[6], DELPHINE SEDDA[6], DONALD NYANGAHU[1], HEATHER JASPAN[1,3], MURRAY SELKIRK[7], KAI TOELLNER[4], VALERIE QUESNIAUX[6], BERNHARD RYFFEL[6], ADAM F CUNNINGHAM[4], FRANK BROMBACHER[1,5] , **WILLIAM GC HORSNELL**[1,4, 6]

[1] INSTITUTE OF INFECTIOUS DISEASE & MOLECULAR MEDICINE & DIVN OF IMMUNOLOGY, UNIVERSITY OF CAPE TOWN & SOUTH AFRICAN MRC [2] FUNDAMENTAL & APPLIED RESEARCH IN ANIMALS AND HEALTH (FARAH), IMMUNOLOGY-VACCINOLOGY, VETERINARY MEDICINE, UNIVERSITY OF LIÈGE, BELGIUM. [3] SEATTLE CHILDREN'S RESEARCH INSTITUTE AND DEPTS OF PEDIATRICS & GLOBAL HEALTH, UNIVERSITY OF WASHINGTON, SEATTLE, USA [4]: MRC CENTRE FOR IMMUNE REGULATION, UNIVERSITY OF BIRMINGHAM, UK; [5] INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY, CAPE TOWNA; [6] LABORATORY OF MOLECULAR & EXPERIMENTAL IMMUNOLOGY AND NEUROGENETICS, UNIVERSITY OF ORLEANS AND LE STUDIUM INSTITUTE FOR ADVANCED STUDIES, ORLÉANS, FRANCE

Maternal immune transfer via nursing is the most significant source of protection from infection in early life. If maternal transfer of immunity by nursing can permanently alter offspring immunity is poorly understood. We identify in this study maternal immune imprinting of offspring nursed by mothers who had a pre-conception helminth infection. Here nursing of pups by helminth exposed mothers transferred protective cellular immunity to these offspring against helminth infection. Notably this protection associated with systemic development of protective Th2 T cell populations which corrected susceptibility to this infection in Th2 impaired IL-4Ra$^{-/-}$ offspring. Protection from infection was also maintained into maturity and associated with incorporation (via nursing) by offspring of maternally derived Th2 competent CD4 T cells. Our data therefore reveals maternal exposure to a globally common source of infection prior to pregnancy provides long-term nursing acquired immune benefits to offspring by their incorporation and maintenance of maternally derived pathogen experienced lymphocytes.
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Programmed DNA elimination in nematodes

JIANBIN WANG and **RICHARD E. DAVIS**

BIOCHEMISTRY AND MOLECULAR GENETICS, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE, USA

Genome maintenance and stability are paramount for organisms. Major genome changes and genome instability can lead to abnormalities, disease, and lethality. While a variety of cellular processes have evolved to ensure genome stability, some organisms have developed mechanisms that lead to regulated genome changes during their life span including a process known as DNA elimination. Programmed DNA elimination in nematodes involves chromosome breakage and loss of chromosome regions in somatic precursor cells during early development while the genome in germline cells remains intact. This leads to distinct germline and somatic genomes in the organism. Comparative genome analysis in ascarids (*Ascaris*, *Parascaris*, and *Toxocara*) demonstrated that 10-90% of the germline genomes are eliminated to form the somatic genomes including the loss of 1,000 – 2,000 genes (5-10% of the genome). The eliminated genes are expressed in the germline suggesting that DNA elimination may be an unusual and irreversible mechanism of gene silencing. The sites of the chromosome breaks occur with very high fidelity leading to the loss of the same sequences in five independent pre-somatic cells and their lineages. Analysis of the chromosome break sites did not identify any sequence or structural motifs, histone modifications, or small RNAs that would specify or recruit machinery to the DNA break sites. We will describe current efforts to understand the molecular mechanism of DNA elimination including developmental timing of the breaks and telomere addition, nature of the breaks, mechanisms that could cause the breaks, and the potential role of nematode specific Argonautes and small RNAs in DNA elimination. Like *C. elegans*, *Ascaris* has holocentric chromosomes in the germline where many centromeres/kinetochores are distributed along the length of the chromosomes. Prior to DNA elimination in the pre-somatic cells, chromosomes regions that will lost lose centromeres/kinetochores. Thus, both dynamic re-localization of centromeres/kinetochores and specific chromosome breaks define which regions of chromosomes will be retained and lost in nematode DNA elimination.

Curation of whipworm genomes by WormBase and the community

FAYE RODGERS[1], MICHAEL PAULINI[2], KEVIN HOWE[2], MATTHEW BERRIMAN[1]

[1] WELLCOME SANGER INSTITUTE, UK [2] EUROPEAN BIOINFORMATICS INSTITUTE, UK.

The human whipworm (*Trichuris trichiura*) is a soil-transmitted helminth that infects an estimated 700 million people worldwide. The genomes of *T. trichiura* and its mouse model, *Trichuris muris*, were first published in 2014, with new, high quality assemblies becoming available more recently. High quality annotation is critical for interpreting genome data but manual curation, the gold standard over computational approaches, is labour intensive and difficult to implement at scale. WormBase is embarking on a programme of manual curation for *T. muris*, with a particular focus on genes implicated in immunomodulation and the early host-pathogen interactions required to establish infections. In addition to our own efforts, we are about to trial a platform to enable the research community to curate gene structures for *T. muris* and other reference genomes. This will be based on a publically available instance of Apollo, a collaborative genome annotation editor. We will describe our approach to integrating community submitted annotations to a canonical gene set. The *T. muris* genome and annotation set will soon be available via the main WormBase portal, facilitating full tracking of all gene model changes. In parallel to this, we have deployed the Apollo platform as part of a ground-breaking public-engagement project in which a cohort of 1000+ non-experts are annotating the *T. trichiura* genome. Using a voting-based mechanism, high quality annotations will be collated for genetic loci that have been reviewed by multiple volunteers. We will present our initial assessment of this novel community-based approach to genome annotation.

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IL-33 deficiency in myeloid APC accelerates helminth-induced Type 2 immunity through impairment of intestinal Treg expansion

KARL HERBINE, LI-YIN HUNG, CHRISTOPHER PASTORE, PAUL BRYCE, **DE'BROSKI R. HERBERT**

DEPARTMENT OF PATHOBIOLOGY, SCHOOL OF VETERINARY MEDICINE, UNIVERSITY OF PENNSYLVANIA

Helminth infections drive expansion of FOXP3^{+} regulatory T cells (T_{regs}) that undergo tissue-specific adaptations for suppression of T effector cells (T_{eff}). It is possible that Treg suppressor activity prolongs host infestation while limiting excessive inflammation and/or tissue damage elicited by parasite infection. This study tested whether interleukin 33 (IL-33), a damage-induced, alarmin, and pro-Type 2 cytokine, served an important role in the regulation of T_{eff} or T_{reg} responses during hookworm infection. Given that professional antigen presenting cells produce IL-33 in certain contexts, we generated mice lacking IL-33 specifically in conventional dendritic cells (DC) (CD11c^{cre} IL-33$^{flox/flox}$) and subjected these animals to two different models of hookworm infection (*Nippostrongylus brasiliensis and Heligmosomoides polygyrus bakerii*). Unexpectedly, our data show that loss of cDC-derived IL-33 augmented worm clearance and Type 2 cytokine production. This enhanced Type 2 immunity in the absence of cDC-derived IL-33 correlated with a selective defect in the frequency of T_{reg} within the mesenteric lymph nodes that drain the intestine, but an increase in T_{reg} frequency within the splenic compartment. Taken together, these data reveal an unexpected, but vital role for DC-derived IL-33 in the local expansion of gastrointestinal T_{reg} in populations that drain the site of GI nematode infection. Ongoing experiments are addressing regulation of APC-derived IL-33 and whether restoration of intestinal T_{reg} accumulation reduces clonal expansion of effector T_H2 cells

Defining the mechanisms of mucosal defence during chronic *Trichuris muris* infection.

CATHERINE SHARPE, DAVID THORNTON & RICHARD GRENCIS

WELLCOME CENTRE FOR CELL-MATRIX RESEARCH, DIVISION OF INFECTION, IMMUNITY AND RESPIRATORY MEDICINE, SCHOOL OF BIOLOGICAL SCIENCES, UNIVERSITY OF MANCHESTER, UK

The intestinal mucosal barrier provides immediate defence against invading pathogens. Recent studies suggest goblet cells and their secretions are key mediators in protecting the host epithelium from damage during gastrointestinal nematode infection. We aimed to analyse the proteome of the large intestinal mucus barrier and determine the goblet cell response during chronic low-dose *T. muris* infection. We provided a comprehensive proteomic analysis of the large intestinal mucus barrier. Mucus extracts from chronically infected *T. muris* C57BL/6 mice had slightly different mucus-associated proteins held within the gel; of interest there was the presence of a serum derived protein called haptoglobin in samples from chronically infected mice, which was not seen during acute *T. muris* infection or homeostasis. We further aimed to elucidate the role of the haptoglobin, as previously this protein has been identified to hold regulatory and antimicrobial roles during active inflammation. We identified that haptoglobin transcripts and protein expression were significantly upregulated at the site of infection during chronic infection. Furthermore, upon analysis of the cellular source of haptoglobin we identified the protein was expressed by neutrophils, which are found invade the site of infection during chronicity. Further exploration in this area could highlight novel effector mechanisms evoked by parasite colonisation to protect the host against parasite induced damage.

Transcriptional profiling reveals a PRRs-mediated recognition of *Haemonchus contortus* in sheep

SI WANG[1], DANDAN HU[1], MIN HU[2], XIANYONG LIU[1], XUN SUO[1]

[1]COLLEGE OF VETERINARY MEDICINE, CHINA AGRICULTURAL UNIVERSITY, CHINA [2]STATE KEY LABORATORY OF AGRICULTURAL MICROBIOLOGY, COLLEGE OF VETERINARY MEDICINE, HUAZHONG AGRICULTURAL UNIVERSITY, CHINA

Control of adaptive immunity by the innate immune system is now a well-established paradigm. Unlike pro-inflammatory stimuli, recognition of helminth products by PRRs skews host immunity to an anti-inflammatory Th2 phenotype. Until now, little is known about whether *Haemonchus contortus*, a major gastrointestinal blood-feeding nematode of ruminants, can be recognized by host PRRs. In this study, we sought to identify PRRs and downstream signaling molecules involved in host's immune responses to *H. contortus* infection. Sheep PBMCs were stimulated with *H. contortus* soluble extracts (HcAg) and transcriptional profiling was performed by RNA-seq. It showed that HcAg upregulated C-type lectin-like receptor (CLR) members and several type 2 immunity-related transcription factors, suggesting the involvement of CLRs-mediated recognition during H. contortus infection. Additionally, HcAg downregulated NOD-like receptor (NLR) downstream signaling molecules, indicating the repression of NLRs-mediated signaling. Overall, our preliminary work showed that an intricate PRRs-mediated recognition network was involved in host immune responses to *H. contortus* infection.

Dynamics of immune cells in the CNS of mice infected by *Trichobilharzia regenti* (Schistosomatidae): implications for parasite clearance

TOMÁŠ MACHÁČEK[1], JAN PANKRÁC[1,2], MARTIN MAJER[1], VLADIMÍR ŠTEIGER[1], KERSTIN IMMIG[3], PETR HORÁK[1]

[1]DEPARTMENT OF PARASITOLOGY, FACULTY OF SCIENCE, CHARLES UNIVERSITY, PRAGUE, CZECHIA; [2]CENTER FOR ADVANCED PRECLINICAL IMAGING, 1ST FACULTY OF MEDICINE, CHARLES UNIVERSITY, PRAGUE; [3]INSTITUTE OF ANATOMY, FACULTY OF MEDICINE, LEIPZIG UNIVERSITY, LEIPZIG, GERMANY

Trichobilharzia regenti is a neuropathogenic schistosome widespread in Europe. It infects the central nervous system (CNS) of vertebrates, such as ducks or mice. While the parasite matures and lays eggs in ducks (definitive hosts), it is eliminated by host immunity in mice (accidental hosts). Clearance of the parasite occurs within a few weeks when peripheral leukocytes infiltrate the affected nervous tissue. We applied flow cytometry to characterize the dynamics of immune cells present in the CNS of mice at several time-points following *T. regenti* infection. The influx of granulocytes and T-lymphocytes into the spinal cord peaked 14 days post infection (dpi) and then vanished by 28 dpi. Microglia expanded throughout the disease, and they represented the major MHC II+ population. Interestingly, granulocytes and T-lymphocytes also infiltrated the brain, mainly 21 dpi, although the brain was mostly free from parasite DNA as revealed by qPCR. Contrary to the spinal cord, expression of MHC II by brain microglia was inconspicuous, suggesting rather "a resting state". Additionally, we examined the role of nitric oxide (NO) in clearance of the parasite. NO can be produced by granulocytes and activated microglia which account for the most prominent cell populations in the spinal cord during the period when the body of the parasite is damaged. However, no effect of NO on parasite mortality and surface or internal tissue damage was noticed after 48-hour *in vitro* incubation with NO-donor. Taken together, granulocytes are the major population of cells infiltrating the spinal cord of mice infected by *T. regenti*, and their role in parasite clearance should be elucidated. NO, as an antiparasitic agent possibly produced by granulocytes, is most likely not harmful to *T. regenti* migrating in the CNS of mice.

Lyz2-specific deletion of IL-4Rα chain in schistosomiasis does not preclude Ly6C^{high} monocytes as the main source of liver macrophages but impairs alternative activation and increase inflammation

MARION ROLOT[1], ANNETTE M. DOUGALL[1], JUSTINE JAVAUX[1], FRANK BROMBACHER[2], BENJAMIN G. DEWALS[1]

[1]IMMUNOLOGY-VACCINOLOGY, UNIVERSITY OF LIÈGE, LIÈGE, BELGIUM. [2]INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE AND DIVISION OF IMMUNOLOGY, UNIVERSITY OF CAPE TOWN, SOUTH AFRICA

M(IL-4) accumulate in liver granulomas of *Schistosoma mansoni*-infected mice from recruited Ly6C^{hi} monocytes and modulate inflammation. Here, we used conditional IL-4 receptor α-chain (IL-4Rα) knockdown *Il4ra*$^{-/lox}$*lyz2*^{Cre} mice to determine whether impairing M(IL-4) modifies the dynamics of Mϕ responses in liver granulomas after *S. mansoni* infection. First, we used reporter *Rosa*^{tdRFP} mice crossed with *lyz2*^{Cre} mice to validate selective Cre-mediated excision in neutrophils and Mϕ in naive and *S. mansoni* infected mice. Next, the liver inflammatory responses were investigated during the first weeks of *S. mansoni* infection. We observed significantly increased total leukocyte numbers, including monocytes, in the liver by week 8 in *Il4ra*$^{-/lox}$*lyz2*^{Cre} mice while these mice survived the infection similarly to hemizygous *Il4ra*$^{-/lox}$ mice. When investigating liver monocyte/Mϕ responses, we observed that CD11b^{lo} resident Küpffer cells (KCs) were severely reducing in term of number over the course of infection and independently of IL-4Rα signalling. While KCs lowered, Ly6C^{hi} monocytes were recruited as soon as week 4 and strongly proliferated by week 8 pi. We further observed that Ly6C^{hi} acquired CD64 expression and converted into Ym1 and Relm-α-expressing CD11b^{hi} Mϕ, while these markers were expressed at significantly low levels in *Il4ra*$^{-/lox}$*lyz2*^{Cre} mice. CD11b^{hi} Mϕ accumulated at the cost of resident CD11b^{lo} KCs, which could suggest that *S. mansoni* infection causes KC disappearance resulting in recruitment of monocytes to the liver. Indeed, ablation of resident KCs in CD169-DTR mice resulted in the accumulation of a CD11b^{hi} Mϕ population similar to the one observed after *S. mansoni* infection. Thus, our findings indicate that *S. mansoni* infection is associated with ablation of resident KCs which could in turn result in the accumulation of M(IL-4) in the liver to control granulomatous inflammation.

Molecular analyses of schistosome reproductive development

JIPENG WANG, RUI CHEN, **JIM COLLINS**

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER, DALLAS, TX, USA

Schistosomiasis is a neglected tropical disease that affects hundreds of millions of the world's poorest people. The pathology of schistosomiasis stems from the fact that these parasites lay hundreds-to-thousands of eggs per day while living in the vasculature. Therefore, understanding the mechanisms that control the development and maintenance of the schistosome reproductive system could present new opportunities to limit the spread of the disease and blunt the pathology caused by the parasite. Interestingly, female schistosome sexual development depends of constant physical contact with a male worm. Although this phenomenon was described almost 100 years ago, there are few molecular insights into how this process is regulated. A major stumbling block for addressing this issue is that the reproductive system of female schistosomes degenerates within days of being removed from the host, making detailed studies of schistosome reproduction challenging**.** Here, we report a novel media formulation that supports male-induced female sexual development and long-term egg production in vitro. Using this media we have discovered a role for a flatworm-specific nuclear receptor that is essential for female reproductive development. We are hopeful the application this new media, together with modern approaches, will allow us to discover new molecules regulating schistosome reproductive development.

Genetic and pharmacological analyses into *Echinococcus multilocularis* stem cells and body axes.

KLAUS BREHM[1], RUTH HERRMANN[1], URIEL KOZIOL[1,2], RAPHAEL DUVOISIN[1], KRISTIN STOLL[1], MARKUS SPILIOTIS[1]

[1]*INSTITUTE OF HYGIENE AND MICROBIOLOGY, UNIVERSITY OF WÜRZBURG, WÜRZBURG, GERMANY;* [2]*UNIVERSIDAD DE LA REPUBLICA, MONTEVIDEO, URUGUAY.*

The lethal zoonosis alveolar echninococcosis is caused by tumor-like growth of the the metacestode larval stage of the fox-tapeworm *E. multilocularis* within host organs. We previously established that parasite growth is exclusively driven by a population of totipotent somatic stem cells and that the invading oncosphere larva temporarily shuts down its anterior pole, leading to metacestode development as posteriorized tissue under control of the wnt signaling pathway. In this work, we further evaluated the role of wnt signaling in metacestode development and demonstrate that RNAi against beta-catenin, the central wnt signaling component, or RNAi against Wnt1/Wnt11 drastically inhibits parasite development. By analyzing gene expression upon beta-catenin RNAi we found evidence for crosstalk between wnt- and BMP/TGF-beta signaling in *Echinococcus*, indicating that the formation of the anterior-posterior and the dorso-vental body axes in the parasite are tightly cross-linked. Interactions between wnt- and BMP/TGF-beta signaling components, as demonstrated using the yeast two-hybrid system, support this hypothesis. We also analyzed signaling pathways that might act upstream of parasite wnt signaling in the formation of brood capsules and protoscoleces and found the expression of hedgehog signaling components preceding the establishment of the anterior pole in metacestode tissue. Finally, we also present evidence for crosstalk between wnt-, BMP/TGF-beta-, hedgehog-, and receptor tyrosine kinase signaling crosstalk acting within the totipotent somatic stem cell population of the parasite. Taken together, our data indicate that information input of multiple *Echinococcus* signaling pathways converge on the parasite's stem cell population to coordinate stem cell self-renewal and differentiation, and to fundamentally modulate body-axis formation in the embryonic oncosphere larva to achieve cancer- and cyst-like growth of the metacestode. This information is important for the development of novel chemotherapeutic measures against alveolar echinococcosis.

Unravelling early host intestinal epithelia interactions with whipworms using intestinal organoids

MARÍA A. DUQUE-CORREA[1], ANAÏS ROUSTANT[1], TAPOKA MKANDAWIRE[1], FERNANDA SCHREIBER[1], DAVID GOULDING[1], PETER NEJSUM[2], RICHARD K. GRENCIS[3], MATTHEW BERRIMAN[1].

[1]WELLCOME SANGER INSTITUTE, WELLCOME TRUST GENOME CAMPUS, HINXTON, UK. [2]DEPT OF INFECTIOUS DISEASES, AARHUS UNIVERSIT , DENMARK. [3] UNIVERSITY OF MANCHESTER, UK.

Whipworms (*Trichuris trichiura*) are soil-transmitted helminths and the etiologic agent of the human disease, trichuriasis. Whipworms live preferentially in the caecum of their hosts where they tunnel through intestinal epithelial cells (IECs) and cause inflammation potentially resulting in colitis. Despite extensive research, the early host IECs-whipworm interactions determining parasite establishment or expulsion remain unclear. Here, we investigate novel host IECs-whipworm interactions during the first events of infection. Imaging caecum of *T. muris* -infected mice (a mouse model of *T. trichuira* infection in humans) during the first three days post infection has revealed whipworm larvae (L1) infecting the epithelium at the base of the crypts of the intestine of mice. These images suggest a close interaction between L1 larvae and the host goblet cells. Based on these data, we hypothesize that targeted infection of goblet cells by L1 larvae can support parasite growth and establishment in the host, potentially by the degradation of mucus. To further understand this critical early colonisation event, we are using intestinal organoids as a replacement model of the murine infections that are currently used. Intestinal organoids are three-dimensional cell clusters generated from human and mouse primary tissue growing *in vitro* and showing similar architecture, cellular composition and function to the gut. Thus far, we have developed and established protocols for generating and differentiating two- and three-dimensional intestinal organoids, derived from either mouse caecum or human inducible pluripotent stem cells; hatching *T. muris* and *T. trichiura* eggs; and exposing or microinjecting organoids with *T. muris* and *T. trichuira* L1 larvae. Using whipworm-infected organoids, we are performing microscopy studies to identify the IECs targeted by the whipworm and visualise active infection. Moreover, we are performing transcriptomic experiments and planning proteomic, flow cytometry and cytokine analysis to discover host IECs-whipworm interactions and evaluate IECs responses to whipworm larvae infection.

Establishment of a novel transgenesis approach to track helminth-specific CD4$^+$ T cells using a 2W1S-expressing model of gastrointestinal nematode infection

BONNIE DOUGLAS[1,2], YUN WEI, XINSHE LI[2], TOM NOLAN[2], JAMES LOK[2], DE'BROSKI HERBERT[1,2]

[1]IMMUNOLOGY GRADUATE GROUP, PERELMAN SCHOOL OF MEDICINE, AND [2]DEPARTMENT OF PATHOBIOLOGY, SCHOOL OF VETERINARY MEDICINE, UNIVERSITY OF PENNSYLVANIA, USA

Approximately one-third of the world is infected with parasitic helminths, and there are currently no available vaccines. Helminths induce robust type 2 immune responses and require CD4$^+$ T cells for clearance, but the chronic persistence of most helminthiases indicates that this response is often insufficient for worm expulsion. Recent work suggests that helminths may evade immune clearance via suppression or dysregulation of CD4$^+$ T cells, but it is not known whether these effects are mediated through TCR-dependent recognition of helminth antigen. To address this question, our lab has generated a novel transgenic line of the gastrointestinal nematode *Strongyloides ratti* to track helminth-specific T cells *in vivo* for the first time. This transgenic line, termed *Hulk*, expresses immunodominant T cell epitope 2W1S as a fusion protein with both a FLAG tag and a green fluorescent protein (GFP) reporter. *Hulk* has been maintained for over 7 generations and stably expresses GFP in all life stages, indicating germline transmission. Moreover, infection of WT C57BL/6 mice with *Hulk* induces nearly a 20-fold expansion of 2W1S tetramer-positive CD4$^+$ T cells in the mesenteric lymph nodes at 14 days post-infection relative to naïve controls. Ongoing studies will evaluate the frequency and phenotype of tetramer-positive CD4$^+$ T cells in the lungs and small intestines as compared to secondary lymphoid organs. Overall, this work describes a technological breakthrough that may provide new insights into understanding helminth-specific T cell responses, which will likely inform vaccine design.

Epigenetic Inheritance in *Schistosoma mansoni* – *Biomphalaria glabrata* interactions

CÉLINE COSSEAU[1] , CHRISTOPH GRUNAU[1] , RONALDO DE CARVALHO AUGUSTO[1], MARION PICARD[1], DAVID ROQUIS[1], AARON TAUDT[2], SARA FNEICH[1], NANCY HOLROYD[3], MATT BERRIMAN[3], SILVAIN PINAULT[1], CRISTIAN CHAPARRO[1], DAVID DUVAL[1], BENJAMIN GOURBAL[1], GUILLAUME MITTA[1]

[1] UNIV. PERPIGNAN VIA DOMITIA, IHPE UMR 5244, CNRS, IFREMER, UNIV. MONTPELLIER, F-66860 PERPIGNAN, FRANCE [2] EUROPEAN INSTITUTE FOR THE BIOLOGY OF AGING, UNIVERSITY OF GRONINGEN, UNIVERSITY MEDICAL CENTRE GRONINGEN, THE NETHERLANDS [3] WELLCOME SANGER INSTITUTE, WELLCOME GENOME CAMPUS, HINXTON, CAMBRIDGESHIRE, UK

Epigenetic mechanisms and chromatin structure play important roles in environmental response and during development. Epigenetic modifications can provide a source of rapid and potentially reversible phenotypic variation. Their impact is therefore expected to be strong in host-parasites interaction for two reasons: (i) rapid co-adaptations between hosts and pathogens are necessary over short evolutionary time scales (ii) parasites often display complex life cycles and multiple, strikingly different, developmental stages which requires high level of developmental plasticity. *Schistosoma mansoni* is a parasitic flatworm and causative agent of intestinal schistosomiasis, this parasite has a complex life cycle involving two consecutive obligate hosts (the gastropod *Biomphalaria glabrata* and a mammal) and two transitions between these hosts as free-swimming larvae. A peculiar aspect of *Schistosomes* biology is their gonochoric status with sexual dimorphism, which is unique among the 20,000 parasitic flatworm species. We will show that (i) the chromatin structure of different developmental stages is characterized by specific changes in chemical modifications of histones, and (ii) that chromatin structure plays important role for the sexual biology of *Schistosoma mansoni*. We will further emphasize (iii) the importance of epigenetic memory in the *Biomphalaria* host by showing how chromatin structures are modified in the mollusk in response to the parasite. Taken together, we provide evidence supporting a prevailing role of epigenetics in the complex life-history transitions that occur in the host-parasite interplay.

Studying the translatome of *Schistosoma mansoni* using ribosome profiling

PATRICK DRIGUEZ, GABRIEL RINALDI, KATE RAWLINSON, MATTHEW BERRIMAN

WELLCOME SANGER INSTITUTE, WELLCOME GENOME CAMPUS, HINXTON, CAMBRIDGESHIRE, UK

Schistosomes infect over 200 million people and are one of the leading causes of morbidity and disability in developing countries. These helminths have a complex life cycle that involves a clonal expansion in the snail host, sexually-differentiated adults in the mammal host and dramatic transitions between free-swimming and parasitic stages. There is indirect evidence that post-transcriptional regulation is responsible for controlling some of these changes over developmental transitions. For example, transcription is halted in the cercarial stage and despite no initial increase in gene transcription after transformation into schistosomulum, protein synthesis expands. It is not known if protein translation is regulated via mRNA sequestration, ribosome pausing, miRNAs or other mechanisms. In addition, current proteomics methods are not yet sensitive enough to detect all proteins synthesised during developmental stages of schistosomes. We are using ribosome profiling to provide a clearer picture of translation across the life cycle. Our first ribosome profiling libraries, using a ligation-free method across a broad range of *S. mansoni* life cycle stages, generated footprints that successfully mapped to CDS regions, revealed codon periodicity, and correlated with published RNA-seq studies. The next step will be to closely examine the cercaria-schistosomulum and miracidium-sporocyst transitions at the mRNA, ribosome footprint and protein levels using RNA-seq, ribosome profiling and quantitative proteomics (LC-MS/MS with TMT labelling), respectively. Following a similar approach, we are also analysing differences between male and female adult worms and the regulation of clock genes in a circadian rhythm study. Once better understood, post-transcriptional regulators or developmental stage critical proteins would make attractive therapeutic targets for schistosomiasis.

Absence of meiotic recombination in the sex chromatin of the nematode *Strongyloides papillosus*.

SIU ZHOU, FELIX BEMM, CHRISTIAN RÖDELSPERGER, **ADRIAN STREIT**

DEPARTMENT OF EVOLUTIONARY BIOLOGY, MAX PLANCK INSTITUTE FOR DEVELOPMENTAL BIOLOGY, TUEBINGEN, GERMANY

Strongyloides sp. alternate between parthenogenetic parasitic and sexual free-living generations. Some species (e.g. S. ratti and S. stercoralis) employ an XX/XO sex determining system. In S. papillosus and S. venzuelensis the X chromosome and one autosome are fused and males are formed by sex specific chromatin diminution, which eliminates the X chromosome derived portion (=diminished region) from one of the two fusion chromosomes.
Coincidentally, we had noticed that there appeared to be no meiotic recombination within the diminished region even during female meiosis. If true, the sex chromatin in *S. papillosus*, different from the autosomal regions in the very same genome, undergoes essentially non-sexual reproduction. This would be expected to have profound consequences for the evolution of this region and might lead to the accumulation of "junk" DNA. Fittingly, the genome of *S. papillosus* had been more difficult to assemble, compared with other *Strongyloides* genomes, because it appears to contain long repetitive regions. First, we used a combination of PacBio and Illumina sequencing to improve the *S. papillosus* genome assembly. Second, by analyzing single male - female crosses, we found no indication for crossing over events between loci located within the diminished region but separated by considerable physical distances. Finally, we whole-genome-sequenced individual *S. papillosus* isolated from the wild and performed linkage analysis. While the autosomal regions appeared to recombine freely, we observed a very strong linkage disequilibrium between all loci in the diminished region, confirming at the population level that there is very little, if any, recombination in this region. In contrast, we readily observed meiotic recombination on the X chromosome in *S. ratti* and we found no indication for linkage disequilibrium over the entire X chromosome, in *S. stercoralis*, indicating, that in this species recombination does occur on their free X chromosomes.

Partial removal of IL-4 receptor alpha within the FoxP3$^+$ regulatory T cell population impairs the control of inflammation in disease

F. BROMBACHER

UNIVERSITY OF CAPE TOWN, SOUTH AFRICA

Signaling via Interleukin-4 receptor alpha (IL-4Rα) mediates Foxp3 regulatory T cells (Tregs) transdifferentiation into ex-Foxp3 Th2 or Th17 cells. We now report that in addition to the *in vitro* ability of IL-4Rα signalling to preserve Treg survival and reinforce Foxp3 expression, partial deletion of IL-4Rα specifically within Foxp3$^+$ Treg population exacerbate immune effector responses resulting in aggravated tissue pathology. This has now been demonstated by us using Foxp3-specific IL-4Ra deficient mice in experimental Type 1 and Type 2 disease models using *Schistosoma mansoni* and *Nippostrongylus brasiliensis*, *Leishmania major*, as well as allergic asthma. Mechanistically, partial abrogation of IL-4Rα signalling within the Foxp3$^+$ Tregs population impaired accumulation of these Tregs to inflamed tissues. Hence, these findings underscore a hitherto unappreciated requirement for IL-4Rα mediated signaling on Foxp3$^+$ Tregs to control inflammatory responses in disease, uncovering the ability of this signaling pathway to positively or negatively regulate Foxp3 Tregs function *in vivo*.

An immunomodulatory parasite limits type 2 inflammation by reprogramming the arachidonic acid metabolism in myeloid cells

MARTA DE LOS REYES JIMENEZ[1], ANTONIE FRIEDL[1], FRANCESCA ALESSANDRINI[1], SONJA SCHINDELA[1], PASCAL HAIMERL[1], DOMINIQUE THOMAS[2], MANUEL KULAGIN[3], YVONNE SCHOBER[4], NATHALIE DEHNE[5], BERNHARD BRÜNE[5], ANDREAS NOCKHER[43], CASPAR OHNMACHT[1], NICOLA L HARRIS[3], JULIA ESSER-VON BIEREN[1]*

[1]CENTER OF ALLERGY AND ENVIRONMENT (ZAUM), TECHNICAL UNIVERSITY OF MUNICH AND HELMHOLTZ CENTER MUNICH; [2]INSTITUTE OF CLINICAL PHARMACOLOGY, GOETHE-UNIVERSITY FRANKFURT, [3]LAB OF INTESTINAL IMMUNOLOGY, ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE, SWITZERLAND; [4]INSTITUTE OF LABORATORY MEDICINE AND PATHOBIOCHEMISTRY, MOLECULAR DIAGNOSTICS, PHILIPPS-UNIVERSITY MARBURG, GERMANY; [5]INSTITUTE OF BIOCHEMISTRY I, GOETHE-UNIVERSITY FRANKFURT, GERMANY

Helminth parasites can modulate immune responses, thus suppressing type 2 inflammation e.g. in allergy. Arachidonic acid-derived lipid mediators are key effector molecules of type 2 inflammation, but if and how helminth parasites may regulate these mediators is unknown. Here, we show that products of a helminth parasite suppress granulocyte recruitment both *in vitro* and during house dust mite allergy *in vivo.* Mixed granulocytes or isolated eosinophils showed reduced expression of chemotactic receptors (e.g. CCR3) after treatment with helminth products, which suppressed granulocyte recruitment in a prostaglandin-dependent fashion. In addition, products of a parasitic nematode fundamentally reprogrammed the lipid mediator profile of human granulocytes as well as of human and mouse macrophages by suppressing pro-inflammatory leukotrienes and inducing regulatory prostaglandins. Finally, we identified NF-κB, p38 and hypoxia inducible factor 1 alpha (HIF1α) as central mechanisms of helminth-driven lipid mediator reprogramming in human macrophages. Our findings suggest that helminths may regulate type 2 immune responses by directly modulating granulocyte activation and recruitment. Thus, treatment with helminth products could be a promising immunomodulatory approach to treat inflammatory diseases with aberrant granulocyte recruitment. Furthermore, products of helminth parasites may modulate type 2 immune responses by reprogramming the arachidonic acid metabolism of myeloid cells.

IL-4 receptor targeting to treat liver fibrosis: Evidence from chronic schistosomiasis in humans, mice and non-human primates

JUSTIN KOMGUEP NONO[1,2,3,4], HLUMANI NDLOVU[2,5], RUTH NYAKUNDI[6], NADA ABDEL AZIZ[1,2,3,7], THABO MPOTJE[1,2,3], SEVERIN KAMDEM[1,2,3], NETONGO P MASUMBE[8,9], SOPHIE GHOMFO[10], DANIELLE SAH[10], SMITREE DABEE[11], MICHAEL SCHOMAKER[12], LUCY OCHOLA[6], THOMAS KARIUKI[6], ROGER MOYOU-SOMO[4], FRANK BROMBACHER[1,2,3]

[1] THE DIVISION OF IMMUNOLOGY, HEALTH SCIENCE FACULTY, UNIVERSITY OF CAPE TOWN, SOUTH AFRICA; [2] CYTOKINES AND DISEASES GROUP, INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY, CAPE TOWN COMPONENT, CAPE TOWN, SOUTH AFRICA; [3] IMMUNOLOGY OF INFECTIOUS DISEASE RESEARCH UNIT, SOUTH AFRICAN MEDICAL RESEARCH COUNCIL (SAMRC), CAPE TOWN, SOUTH AFRICA; [4] THE MEDICAL RESEARCH CENTRE, INSTITUTE OF MEDICAL RESEARCH AND MEDICINAL PLANT STUDIES (IMPM), MINISTRY OF SCIENTIFIC RESEARCH AND INNOVATION, YAOUNDÉ, CAMEROON; [5] DEPARTMENT OF INTEGRATIVE BIOMEDICAL SCIENCES, HEALTH SCIENCES FACULTY, UNIVERSITY OF CAPE TOWN; [6] INSTITUTE OF PRIMATE RESEARCH, NATIONAL MUSEUMS OF KENYA, NAIROBI, KENYA; [7] BIOTECHNOLOGY/BIOMOLECULAR CHEMISTRY PROGRAM, CHEMISTRY DEPARTMENT, FACULTY OF SCIENCE, CAIRO UNIVERSITY, CAIRO, EGYPT; [8] THE BIOTECHNOLOGY CENTRE AND DEPARTMENT OF BIOCHEMISTRY, FACULTY OF SCIENCE, UNIVERSITY OF YAOUNDÉ 1, CAMEROON; [9] PATHOLOGY LAM LAB, SCHOOL OF MEDICINE, UNIVERSITY OF UTAH, USA; [10] UNIVERSITE DES MONTAGNES, BANGANGTE, CAMEROON; [11] DIVISION OF MEDICAL VIROLOGY, DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAPE TOWN; [12] CENTRE FOR INFECTIOUS DISEASE EPIDEMIOLOGY AND RESEARCH, SCHOOL OF PUBLIC HEALTH AND FAMILY MEDICINE, UNIVERSITY OF CAPE TOWN, SOUTH AFRICA

Fibroproliferative diseases are the leading cause of human mortality globally. Despite their pathophysiological differences, this group of diseases associates with myofibroblast activation, collagen deposition and fibrosis, a cascade of events that can be initiated and amplified by type 2 cytokines. Central to the production of type-2 cytokines is the host signaling via the IL-4 receptor alpha (IL-4Rα). A pathogenic role has therefore been suggested for the signaling via IL-4Rα in fibroproliferative diseases like allergy and schistosomiasis. However, the therapeutic value of targeting IL-4Rα has only been successfully addressed in the former but not the latter disease. In school children from a schistosomiasis-diseased area in rural Cameroon, abdominal ultrasound analyses combined with *il-4r* gene mass array screens revealed a considerably increased liver IP score in children with a gain-of-function S503P SNP of the interleukin-4 receptor gene (rs1805015) arguing for a pathogenic role of the signaling via this receptor on chronic schistosomiasis-driven liver fibrosis. Furthermore, using a new and tractable murine model of inducible cessation of IL-4Rα mediated signaling, we demonstrate that cessation of IL-4Rα mediated signaling abrogates already initiated type-2 immune responses during chronic murine schistosomiasis and considerably reduced the egg-surrounding collagen as well as the total collagen content in the liver without affecting the viability of the infected animals confirming a beneficial effect of targeting IL-4Rα in preclinical settings to mitigate liver fibrosis. To further validate these observations, we will also report on the recently initiated testing of anti-sense oligonucleotides designed to specifically inhibit *il-4rα* gene transcripts in non-human primate models of chronic schistosomiasis. Overall, our observations on the possible anti-fibroproliferative potential of targeting il-4 receptor during chronic schistosomiasis will be discussed.

High-throughput expression of the hookworm recombinant secretome for an *in vivo* screen to find novel therapeutics to treat Inflammatory Bowel Disease

STEPHANIE RYAN[1], [1]GIACOMIN, P., [1]FIELD, M., [3]JOHNSON, W., [1]NAVARRO, S., [1]SOTILLO, J., [1]PICKERING D., [2]MITREVA, M., [3]ALEXANDROV, K., [1]LOUKAS, A.

[1]AUSTRALIAN INSTITUTE OF TROPICAL HEALTH & MEDICINE, JAMES COOK UNIVERSITY, CAIRNS, QLD, AUSTRALIA; [2]MCDONNELL GENOME INSTITUTE, WASHINGTON UNIVERSITY, SAINT LOUIS, MO, USA; [3]INSTITUTE OF MOLECULAR BIOSCIENCES, THE UNIVERSITY OF QUEENSLAND, BRISBANE, AUSTRALIA

Parasitic infections place a costly and disproportionate disease burden on developing countries. However, evidence suggests that certain parasites, such as hookworms, offer substantial health benefits for diseases that result from a dysregulated immune response, typified by allergy and autoimmunity. Helminth therapy is gaining momentum and widespread acceptance in the medical community, although the use of live hookworm therapeutics has drawbacks. An increasing body of evidence suggests that a safer option is to harness the immunomodulatory properties of the hookworm's excretory/secretory (ES) complement. We and others have shown that ES proteins protect against inflammation in several mouse models of colitis. We therefore developed a high-throughput bioinformatics analysis pipeline to profile and identify candidate protective proteins found in the *A. caninum* ES proteome., In order to rapidly generate and screen large numbers of recombinant hookworm proteins for immunomodulatory activity *in vivo,* we utilized a *Leishmania* cell-free protein expression system to generate ~0.5 ml of each recombinant protein fused to GFP. One hundred recombinant ES proteins in the form of (crude ribosomal lysates) were administered to mice (n=5 per protein) to assess their anti-inflammatory properties in a model of acute colitis. After robust statistical filtering, 21 proteins were found to confer significant protection against various parameters of colitis. Lead proteins were expressed in yeast and purified, and their bioactivity validated in: (1) two discrete models of colitis, and (2) human PBMC cytokine profiling. This study has established a novel and rapid biologics discovery pipeline from bioinformatics to *in vivo* validation, and has identified a comprehensive library of hookworm derived immunotherapeutics for treating the global burden of inflammatory diseases.

Is the *Acanthocheilonema viteae*-derived immunomodulator ES-62 an elixir of life for the male of the species?

WILLIAM HARNETT[1], FELICITY LUMB[1], JENNY CROWE[2], JAMES DOONAN[1], MARC HUBNER[3], COLIN SELMAN[4], MARGARET HARNETT[2]

[1]STRATHCLYDE INSTITUTE OF PHARMACY AND BIOMEDICAL SCIENCES, UNIVERSITY OF STRATHCLYDE, GLASGOW U.K. [2]INSTITUTE OF INFECTION, IMMUNITY AND INFLAMMATION, GLASGOW BIOMEDICAL RESEARCH CENTRE, UNIVERSITY OF GLASGOW , U.K. [3] INSTITUTE OF MEDICAL MICROBIOLOGY, IMMUNOLOGY AND PARASITOLOGY, UNIVERSITY OF BONN, GERMANY. [4]GLASGOW AGEING RESEARCH NETWORK, INSTITUTE OF BIODIVERSITY, ANIMAL HEALTH AND COMPARATIVE MEDICINE, UNIVERSITY OF GLASGOW, UK

The average lifespan in industrialised countries has recently greatly increased due to improved medication, sanitation and nutrition. Health-span has not similarly increased however: rather, fuelled by the high prevalence of obesity, there has been an upsurge in age-related diseases like atherosclerosis, cardiovascular disease and type 2 diabetes. Recent findings that ageing and obesity are associated with chronic, low-grade inflammation and gut dysbiosis has sparked interest in the idea that parasitic worms, via secretion of anti-inflammatory products, can protect against these conditions. We are therefore investigating whether one such product, ES-62, a phosphorylcholine-containing glycoprotein secreted by the filarial nematode *Acanthocheilonema viteae*, can increase the health- and lifespan of mice fed a high fat diet (HFD). ES-62 (1 μg/dose) was administered subcutaneously weekly to HFD-fed C57/BL6 mice and animals were examined 160, 340 and 500 days later for effects on a range of age-, inflammation- and obesity-related parameters. ES-62 was found to enhance the levels of eosinophils, cells that play a key role in metabolic homeostasis in adipose tissue and are greatly reduced in obesity, in the white adipose tissue (WAT) of mice compared with PBS-treated controls. This effect was accompanied by increased gene expression of IL-5 and IL-13 in female WAT and reduced IL-1β and IL-6 expression in male WAT. Additionally, ES-62-treated mice showed reduced expression of the fat lipolysis transcriptional regulator Trip-B2 and increased expression of the adipocyte beigeing marker UCP1. ES-62 also slowed the ageing-associated decline in mitochondrial function and suppressed HFD-induced gut inflammation. A number of gender-specific effects were observed and strikingly, ES-62 appears to increase the longevity of HFD-fed male, but not female mice. Overall, these results indicate that ES-62 may act to limit pathological inflammation and maintain metabolic homeostasis in obese adipose tissue with subsequent benefits for both health-span and lifespan.

An iterative approach to the development of novel therapeutics against human schistosomiasis

MEGHAN GUZMAN[1], REID TARPLE[Y2], ALEXANDER B. TAYLOR[3], FRÉDÉRIC CHEVALIER[4,] STANTON F. MCHARDY[2], TIMOTHY J. ANDERSON[4], **PHILIP T. LOVERDE[3]**

[1]DEPT OF MICROBIOLOGY, IMMUNOLOGY & MOLECULAR GENETICS, UT HEALTH SAN ANTONIO, TEXAS; [2]CENTER FOR INNOVATIVE DRUG DISCOVERY, SAN ANTONIO; [3]DEPT OF BIOCHEMISTRY & STRUCTURAL BIOLOGY, UT HEALTH SAN ANTONIO; [4]TEXAS BIOMEDICAL RESEARCH INSTITUTE, SAN ANTONIO, TEXAS, USA

Human schistosomiasis is a debilitating, life-threatening disease affecting more than 250 million people in as many as 78 countries. Currently, schistosomiasis is labeled a neglected tropical disease and is second only to malaria as "the most devastating parasitic disease". There is only one drug of choice effective against all three major species of Schistosoma, Praziquantel (PZQ). However, as with many monotherapies, resistance is emerging in the field and can be selected for in the laboratory. Previously used therapies include Oxamniquine (OXA), however shortcomings such as affordability resulted in discontinuation. Our collaborations with medicinal chemists and structural biologists have enabled us to develop and test novel drug derivatives of OXA to treat this disease. Using an iterative process for drug development, we have successfully identified one derivative that is effective against all three species of the parasite at varying levels and shows promising preliminary in vivo efficacy, CIDD-0066790. As CIDD-0066790 is a racemic mixture, we have isolated the R and S enantiomers of this derivative and identified the R form as most effective. Furthermore, we have identified three more efficacious derivatives, one of which CIDD-0072398 kills 100% of S. mansoni worms. We will present data on the in vitro and in vivo efficacy of these 3 novel drugs. Our goal is to generate a secondary therapeutic that can be used in conjunction with Praziquantel to overcome the ever-growing threat of resistance. In this regard we are testing our best derivatives in conjunction with PZQ to determine efficacy of combination therapy. The ability and need to design, screen, and develop future, affordable therapeutics to treat human schistosomiasis is critical for successful control program outcomes.

Insect biotechnology meets schistosomes – the lethal effect of ladybird-derived harmonine on *Schistosoma mansoni*

SIMONE HAEBERLEIN[1], JOSINA KELLERSHOHN[1], LAURA THOMAS[2], BERNHARD SPENGLER[3], ARNOLD GRÜNWELLER[2], ANDREAS VILCINSKAS[4], CHRISTOPH G. GREVELDING[1]

[1]INSTITUTE OF PARASITOLOGY, BFS, JUSTUS-LIEBIG-UNIVERSITY GIESSEN; [2] INSTITUTE OF PHARMACEUTICAL CHEMISTRY, PHILIPPS UNIVERSITY MARBURG; [3]INSTITUTE OF INORGANIC AND ANALYTICAL CHEMISTRY, JUSTUS-LIEBIG-UNIVERSITY GIESSEN; [4]INSTITUTE FOR INSECT BIOTECHNOLOGY, JUSTUS-LIEBIG-UNIVERSITY GIESSEN; DEPARTMENT BIORESOURCES, FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY (IME)

Insects represent an innovative source for the discovery of novel antiparasitic compounds. Harmonine is an antimicrobial compound discovered in the invasive Asian ladybird *Harmonia axyridis*. Pilot studies have shown that harmonine has a remarkable all-round activity against mycobacteria and protozoans such as *Plasmodium* and *Leishmania* parasites. To explore the anthelminthic potential of harmonine for platyhelminths, we tested its effect on *Schistosoma mansoni*. *In vitro* studies showed that harmonine was lethal to adult *S. mansoni* at concentrations as low as 10 µM. With 5 µM, the motility of worms was reduced to a minimum, female and male worms separated, and egg production was fully abolished. Tegument blisters and prominent gut dilatations were observed. Confocal microscopy revealed structural disintegration of the male and female reproductive organs, including reduced sperm numbers and a reduction proliferating gonadal stem cells, which might point to a cellular target of harmonine involved in gonad development or function. *In silico* modeling suggested acetylcholinesterase (AChE) as one possible target of harmonine. Indeed, harmonine inhibited recombinant AChE and first experiments also suggest a partial inhibition of the acetylcholine-hydrolyzing activity in protein extracts of *S. mansoni*. Two different orthologues of AChE were found to be expressed in adult worms, and comparative RNA-seq as well as qPCR analyses revealed interesting pairing-dependent expression differences in female worms. In summary, next to its antimicrobial and antiprotozoal effects, harmonine has also anti-schistosomal activity. These findings promote this natural compound as an attractive candidate for further development. Whether other helminth species, such as the liver fluke *Fasciola hepatica*, are also affected by harmonine is currently under investigation.

Identification and Profiling of Anthelmintic Compounds in Veterinary Parasitology

PAUL M. SELZER

BOEHRINGER-INGELHEIM VETMEDICA GMBH, BINGER STR 173, 55216 INGELHEIM AM RHEIN, GERMANY

Infections with parasitic helminths are responsible for a significant part of the parasitic burden in humans, animals, and plants. They cause devastating diseases and drastic economic losses in agriculture. Several anthelmintic drugs are on the market to combat the parasites and to treat the respective diseases. Although those drugs have been effective in eliminating nematodes and filarial parasites, increasing drug resistance makes their continued use of less value. Therefore, the discovery and development of novel anthelmintic drugs is essential. Physiology-based whole organism *in vitro* assays are important for the identification and profiling of novel anthelmintic compounds in veterinary medicine. Using these phenotypic assays, large compound libraries can be screened to identify hits and lead structures active against gastrointestinal and filarial parasites. In addition, target based screens can also discover anthelmintic hits and lead compounds. Many of these compounds cause distinct phenotypic changes with respect to morphology and locomotion of the treated parasites. By discovering the specific mode of action (MoA) of the most promising compounds, it is possible to link the compounds activity to the related phenotype and consider this a genotype-to-compound-to-phenotype correlation. From our experience, we conclude that a combination of physiology- and target-based approaches will increase the drug discovery output, which is desperately needed to over come resistance.

Epithelial cell-derived phospholipase A_2 group 1B (PLA_2g1B) is an endogenous anthelmintic

LEWIS J. ENTWISTLE[1], VICTORIA S. PELLY[1], STEPHANIE M. COOMES[1], YASHASWINI KANNAN[1], JIMENA PEREZ-LLORET[1], STEPHANIE CZIESO[1], MARIANA SILVA DOS SANTOS[2], JAMES I. MACRAE[2], LUCY COLLINSON[3] ABDUL SESAY[4], NIKOLAY NIKOLOV[4], AMINA METIDJI[5], HELENA HELMBY[6], DAVID Y. HUI[7] AND **MARK S. WILSON**[1,8]

[1]ALLERGY AND ANTI-HELMINTH IMMUNITY LABORATORY, [2]METABOLOMICS, [3]ELECTRON MICROSCOPY, [4]ADVANCED SEQUENCING FACILITY, [5]AHR IMMUNITY LABORATORY, THE FRANCIS CRICK INSTITUTE, LONDONT, UK. [6]DEPARTMENT OF IMMUNOLOGY AND INFECTION, LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, LONDON, UK. [7]DEPARTMENT OF PATHOLOGY, METABOLIC DISEASE RESEARCH CENTER, UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE, CINCINNATI, OHIO, 45237, USA. [8]IMMUNOLOGY DISCOVERY, GENENTECH INC., SOUTH SAN FRANCISCO. CA. 94080. USA.

Immunity to intestinal helminth infections has been well studied, however the mechanism of helminth killing prior to expulsion remains unclear. Here we identify epithelial cell-derived phospholipase A_2 group 1B (PLA_2g1B) as a host-derived endogenous anthelmintic. PLA_2g1B is elevated in resistant mice and responsible for killing tissue-embedded larvae. Despite comparable activities of other essential type 2-dependent immune mechanisms, *Pla2g1b*$^{-/-}$ mice failed to expel the intestinal helminths *Heligmosomoides polygyrus* or *Nippostrongylus brasiliensis*. Expression of *Pla2g1b* by epithelial cells was dependent upon intestinal microbiota, adaptive immunity and common-gamma chain-dependent signaling. Notably, *Pla2g1b* was down-regulated in susceptible mice and inhibited by IL-4R-signalling in vitro, uncoupling parasite killing from expulsion mechanisms. Resistance was restored in *Pla2g1b*$^{-/-}$ mice by treating infective *H. polygyrus* L3 larvae with PLA_2g1B, which reduced larval phospholipid abundance. These findings uncover epithelial cell-derived *Pla2g1b* as an essential mediator of helminth killing, highlighting a previously overlooked mechanism of anti-helminth immunity.

Nematode secreted cholinesterases and cholinergic regulation of immunity

MURRAY E. SELKIRK[1], LUKUS ROBERTS[1], CORINNA SCHNOELLER[1], MATTHEW DARBY[2], CLARE MACKOWIAK[3], DELPHINE SEDDA[3], VALERIE QUESNIAUX[3], BERNHARD RYFFEL[2,3], RACHEL VAUX[1], RITA BERKACHY[1], KLEONIKI GOUNARIS[1], AND WILLIAM G. HORSNELL[2,3,4]

[1]DEPT OF LIFE SCIENCES, IMPERIAL COLLEGE, LONDON, UK; [2]DIVISION OF IMMUNOLOGY, UNIVERSITY OF CAPE TOWN, SOUTH AFRICA; [3] LABORATORY OF MOLECULAR AND EXPERIMENTAL IMMUNOLOGY AND NEUROGENETICS, UNIVERSITY OF ORLEANS AND LE STUDIUM INSTITUTE FOR ADVANCED STUDIES, ORLÉANS, FRANCE; [4]INSTITUTE OF MICROBIOLOGY AND INFECTION, UNIVERSITY OF BIRMINGHAM, UK

Many parasitic nematodes which colonise mucosal surfaces secrete acetylcholinesterases (AChEs), although the function of these enzymes is not known. We have observed that Group 2 innate lymphoid cells (ILC2s) synthesise and release acetylcholine during parasitic nematode infection. The cholinergic phenotype of pulmonary ILC2s defined by expression of choline acetyltransferase (ChAT) was associated with their activation state, could be induced by *in vivo* exposure to the alarmin cytokines IL-33 and IL-25, and was augmented by interleukin (IL)-2 *in vitro*. Disruption of ChAT expression in ILC2s via generation of RORa^{Cre}ChAT^{LoxP} transgenic mice rendered these animals more susceptible to infection with *Nippostrongylus brasiliensis* than ChAT^{loxp} controls, and was associated with reduced IL-13 production in both ILC2s and CD4+ T cells. This defect in immunity was asociated with loss of ChAT activity in ILC2s, as adoptive transfer of pulmonary ILC2s from ChAT^{loxp} into RAG2$^{-/-}$IL-2rg$^{-/-}$ recipients resulted in reduction of worm burdens, whereas transfer of those from RORa^{Cre}ChAT^{LoxP} donors did not. These data show that synthesis of acetylcholine by ILC2s is important for initiating and potentiating type 2 immunity and suggest a functional role for ILC2-derived acetylcholine in induction of type 2 effector functions in the lung.

Argonomics: A Systematic Analysis of Argonaute Proteins and Small RNA Pathways in *C. elegans*

URI SEROUSSI, ANDREW LUGOWSKI, **JULIE M. CLAYCOMB**

DEPARTMENT OF MOLECULAR GENETICS, UNIVERSITY OF TORONTO, CANADA

RNA interference (RNAi) pathways, consisting of Argonaute effector proteins and small RNA molecules (18-30nt) that provide sequence specificity, play key roles in gene regulation across all domains of life. Argonaute proteins are the conserved engines of RNAi pathways, and although they were initially characterized as post-transcriptional modulators of gene expression, studies of Argonautes in a wide array of species have revealed that they impact gene expression at nearly every stage in the life cycle of a transcript—from transcription to nuclear export and translation. Because of their central role in RNAi and profound impact on the development and differentiation in a wide array of organisms, uncovering new and conserved molecular mechanisms of Argonautes advances our fundamental knowledge of cellular homeostasis and has the potential for more precise means to manipulate gene expression, relevant for biotechnology and therapeutics. *C. elegans* has long been a champion of RNAi research, and remarkably, its genome encodes 27 Argonaute genes, 22 of which appear to encode functional proteins. Our team has applied a powerful constellation of cutting-edge genetic, genomic, cell and molecular biology approaches to develop an integrated portrait of the molecular mechanisms of 22 mostly uncharacterized Argonaute proteins throughout worm development. Utilizing CRISPR/Cas9 mediated genome-editing, we have epitope-tagged all 22 Argonautes with GFP-3xFLAG to visualize their differential spatial and temporal expression patterns throughout development. Using small RNA immunoprecipitation sequencing, we have made significant progress in defining the unique and overlapping complements of small RNAs bound by each Argonaute. Furthermore, our phenotypic analysis of *ago* mutants has revealed previously unappreciated phenotypes; for instance *wago-1*, *wago-4*, *ppw-2* and *hrde-1* display a Mortal germline (Mrt) fertility defect at elevated temperatures. Thus, our pioneering studies will clearly provide an unprecedented view of the intricacies of small RNA pathway activity throughout the development a complex animal.

Nematode microRNAs – roles in development and host-parasite interactions

COLLETTE BRITTON, ALAN WINTER, NEIL MARKS, HENRY GU, KIRSTY MAITLAND, VICTORIA GILLAN, EILEEN DEVANEY

INSTITUTE FOR BIODIVERSITY, ANIMAL HEALTH AND COMPARATIVE MEDICINE, UNIVERSITY OF GLASGOW, UK

The mechanisms regulating development and survival of parasitic helminths within their hosts are not well understood. We are examining microRNAs in parasitic nematodes to investigate potential roles in development and immune modulation. microRNAs (miRNAs) are small (~22 nucleotide) non-coding RNAs that regulate gene expression at the post-transcriptional level. They are expressed in a diverse range of organisms from viruses to humans. We previously identified 192 miRNAs in the ovine gastrointestinal nematode *Haemonchus contortus* and, using microarray analysis, have begun to examine the functions of these. Two miRNAs are enriched in the infective L3 larval stage and genetic knockout of the homologous miRNAs in the free-living nematode *Caenorhabditis elegans* prevents arrest as dauer stage larvae, considered analogous to parasite infective L3. The two miRNAs are predicted to suppress metabolic processes associated with development and our studies in *C. elegans* indicate that they may act in parallel to the insulin signaling pathway to regulate developmental progression. In contrast to the L3 stage, many novel miRNAs are upregulated in the L4 and adult stages of *H. contortus*. Using small RNA sequencing we have identified that some of these are present in excretory-secretory (ES) products and in extracellular vesicles (EVs) released from L4 and adult worms in vitro. Secreted miRNAs can also be detected in abomasal tissue from *H. contortus* infected sheep and we speculate that these may modulate immune outcome. Our results indicate that miRNAs play important roles in development and in host-parasite interactions and identify miRNAs and the pathways they regulate as potential targets of parasite control.

Genetic analysis of biomedically important traits in Schistosomes

TIM ANDERSON

TEXAS BIOMEDICAL RESEARCH INSTITUTE, SAN ANTONIO, TEXAS, USA

Schistosomes provide a surprisingly tractable system for experimental genetics. The complete lifecycle can be maintained in the laboratory and seventy five years of elegant experimental work have revealed heritable variation in a wide range of biomedically important and biologically interesting traits including host specificity, virulence, and drug resistance. We now have an excellent genome assembly, and developing functional and cell biology tool kits, while population genomic data is easily collected from field collected parasites. My lab combines experimental genetic crosses and linkage analyses, genome wide association, population genomics and functional analyses to understand the genetic basis of key schistosome traits. I showcase several ongoing projects in my lab.

Kinases and GPCRs of *Schistosoma mansoni*, a subtranscriptomics-based overview about their potential functions for schistosome biology with implications for basic and applied research

CHRISTOPH G. GREVELDING[1], STEFFEN HAHNEL[1,7], SIMONE LANGNER[1], THOMAS QUACK[1], COLETTE DISSOUS[2], NICOLAS J. WHEELER[3], TIMOTHY A. DAY[3], PAUL MCVEIGH[4], ARPORN WANGWIWATSIN[5], NANCY HOLROYD[5], MATTHEW BERRIMAN[5], PAULA RIBEIRO[6†], ZHIGANG LU[1,5]

[1]INSTITUTE OF PARASITOLOGY, JUSTUS-LIEBIG-UNIVERSITY GIESSEN, GERMANY; [2]CENTER FOR INFECTION AND IMMUNITY OF LILLE, INSTITUT PASTEUR LILLE, FRANCE; [3]COLLEGE OF VETERINARY MEDICINE, IOWA STATE UNIVERSITY, USA; [4]THE INSTITUTE FOR GLOBAL FOOD SECURITY, , QUEEN'S UNIVERSITY, BELFAST, UK; [5]WELLCOME TRUST SANGER INSTITUTE, UK; [6]INSTITUTE OF PARASITOLOGY, MCGILL UNIVERSITY, MONTREAL, CANADA; [7]DEPT OF MOLECULAR BIOSCIENCES, NORTHWESTERN UNIVERSITY, USA

As one of the exceptional biological features of schistosomes, the adult female achieves sexual maturation only if it is constantly paired with the male. Although the male is sexually mature before pairing, it is assumed that the male-female interaction of schistosomes is a bidirectional process. However, not much is known about the complexity of pairing-dependent gene expression, especially with respect to the gonads. Based on an established organ-isolation approach and subsequent transcriptomics with RNA of ovaries and testes from both paired and unpaired adult *S. mansoni* we identified transcripts of >7,000 genes in the gonads of both sexes. Although transcript levels of the majority of these genes (>4,000) were pairing-unaffected in both gonads, transcripts of 3,600 (ovaries) and 243 (testes) genes occurred pairing-dependently. Among these, 309 and 42 differentially transcribed genes showed ovary-specific and testis-specific transcriptional activity, respectively. Bioinformatics analyses of these data sets provided a comprehensive overview of the *S. mansoni* kinome. According to our re-analysis it consists of 357 kinases in total, of which 268 represent protein kinases (pks) and 83 non-protein kinases (non-pks) transcribed in adult *S. mansoni*. Remarkably, many of the adult-stage pk and non-pk genes exhibited a pairing-dependent and gonad-preferential transcript occurrence. In schistosomes GPCRs represent the largest receptor family comprising 115 receptors in *S. mansoni*. Of these 60% are transcribed in adults, covering all classes according to a new GPCR phylogeny. Detailed bioinformatics based on our transcriptomics data provided unexpected clues for potential roles of GPCRs in schistosome biology and especially male-female interaction, which included gonad-unrelated but pairing-dependent processes. Finally, a first GPCR-selective *in silico* comparison to *Fasciola* genome data revealed a high congruence between both GPCR*omes*. Because kinases as well as GPCRs represent molecules attractive as potentially druggable targets, the results presented will be of relevance for both basic and applied parasitology research.

Serine/threonine protein phosphatase 1 (PP1) controls growth and reproduction in *Schistosoma japonicum*

LU ZHAO[1], ZHIGANG LU[2], XIN HE[1], MUDASSAR N. MUGHAL[1], RUI FANG[1], YANQIN ZHOU[1], J UNLONG ZHAO[1], ROBIN B. GASSER[1,3], CHRISTOPH G. GREVELDING[2], QING YE[1], **MIN HU**[1]

[1]HUAZHONG AGRICULTURAL UNIVERSITY, WUHAN, CHINA. [2]JUSTUS-LIEBIG-UNIVERSITY GIESSEN, GIESSEN, GERMANY. [3]THE UNIVERSITY OF MELBOURNE, VICTORIA, AUSTRALIA

Schistosome reproduction is a target for discovering or designing much needed new drugs against schistosomiasis, a potentially fatal infectious disease of humans with worldwide importance. Schistosomes are dioecious, and the sexual maturation of females depends on pairing with males. Although protein kinases have been shown to be indispensable for reproductive development of schistosomes, the roles of protein phosphatases in this process are poorly understood. Given the important roles of serine/threonine protein phosphatase 1 (PP1) in cell-cycle progression and male reproduction in mammals, we explored three genes encoding catalytic subunits of serine/threonine protein phosphatase 1 (PP1c) that were structurally and evolutionarily conserved in *Schistosoma japonicum*. *In-situ* hybridization showed transcripts of three *Sj-pp1c* genes mainly co-localized in the reproductive organs and tissues. Triple-knockdown of *Sj-pp1c* genes by RNAi caused stunted growth and decreased pairing stability of worm pairs, as well as remarkable reduction in cell proliferation activity and defects in reproductive maturation and fecundity. Transcriptomic analysis post RNAi indicated that *Sj-pp1c* genes are involved in controlling worm development and maturation by regulating cell proliferation, egg-shell synthesis, nutritional metabolism, cytoskeleton organization, and neural processes. Our study represents the first comprehensive functional characterization of a family of protein phosphatase in schistosomes, provides new insights into the functions of PP1c in worm growth and reproduction, and contributes to a better understanding of the molecular mechanisms controlling the reproductive biology of schistosomes. It also opens new perspectives on the development of disease intervention strategies.

Comparative transcriptomic analysis shows molecular mechanisms used by visceral and neurotropic avian schistosomes.

[1]**ROMAN LEONTOVYČ**, [2]NEIL YOUNG, [1,3]MARTIN KAŠNÝ, [2]ROBIN GASSER, [1]PETR HORÁK

[1]DEPARTMENT OF PARASITOLOGY, FACULTY OF SCIENCE, CHARLES UNIVERSITY, PRAGUE, CZECH REPUBLIC, [2]FACULTY OF VETERINARY SCIENCE, UNIVERSITY OF MELBOURNE, AUSTRALIA, [3]DEPARTMENT OF BOTANY AND ZOOLOGY, FACULTY OF SCIENCE, MASARYK UNIVERSITY, BRNO, CZECH REPUBLIC

Avian schistosomes of the genus *Trichobilharzia* are in focus of parasitologists due to medical importance of cercarial dermatitis they cause to humans. In addition, *T. regenti* causes neuropathogenic effects on its permissive avian hosts and accidental mammalian hosts. To date mainly human pathogens of the genus *Schistosoma* are intensively studied, and the other schistosomatids are somewhat neglected in terms of molecular investigations. *Trichobilharzia szidati* and *T. regenti* belonging to the same genus differ in their life strategy in definitive hosts. Similarly to human schistosomes, *T. szidati* schistosomula migrate via circulatory system to the lungs, liver and visceral veins. On the other hand, *T. regenti* undergoes a unique neurotropic migratory route via peripheral nerves, the spinal cord, and brain up to the nasal mucosa. Using light microscopy and transmission electron microscopy, the lung schistosomula (*T. szidati*) and schistosomula in the spinal cord (*T. regenti*) have been explored for their localization in the tissues, interaction with the host and nutrition preference. Results have been confronted with transcriptomic data of two consecutive stages, cercariae and schistosomula of both species, to elucidate the spectra of proteins in the early and late phases of infection. Despite the same mission of cercariae of both species, i.e., to find and attack the definitive host, transcription profiles differ in, e.g., ribosomal proteins, and components of energy and lipid metabolisms. Differences between schistosomulum stages have been observed in, e.g., signaling, transport system and regulation of transcription. Also, the detailed expression profiles of peptidases have been compared and linked to different nutrition preferences of both species. Our results provide new insights into the molecular biology of avian schistosomes and can be used as a comparative platform for the research of schistosomatids and other trematodes.

Population differences in vaccine responses: do parasitic infections contribute?

ALISON ELLIOTT

MEDICAL RESEARCH COUNCIL/UGANDA VIRUS RESEARCH INSTITUTE AND LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE UGANDA RESEARCH UNIT, ENTEBBE, UGANDA

There is evidence of geographical variation in vaccine response for a number of important licenced and investigational vaccines. Responses tend to be lower in low-income and tropical countries. Live vaccines may be affected more than inert vaccines. Animal models suggest that immunomodulation by parasites has a role, but the extent to which parasitic infections contribute to differences between human populations, and whether interventions against parasites can improve vaccine responses and efficacy is not known. Approaches to addressing this will be discussed.

The *Schistosoma mansoni* glycoprotein omega-1 improves whole-body metabolic homeostasis independent of its Th2 polarizing capacity

HENDRIK VAN DER ZANDE[1,4], MICHAEL GONZALEZ[4], MARISKA VAN HUIZEN[1], KARIN DE RUITER[1], RUUD WILBERS[3], LOTTE WESTERHOF[3], ARJEN SCHOTS[3], P'NG LOKE[4], MARIA YAZDANBAKHSH[1], BRUNO GUIGAS[1,2]

[1] *DEPARTMENT OF PARASITOLOGY AND* [2] *DEPARTMENT OF MOLECULAR CELL BIOLOGY, LEIDEN UNIVERSITY MEDICAL CENTER, LEIDEN* [3] *LABORATORY OF NEMATOLOGY, WAGENINGEN UNIVERSITY AND RESEARCH, WAGENINGEN, THE NETHERLANDS* [4] *DEPARTMENT OF MICROBIOLOGY, NEW YORK UNIVERSITY SCHOOL OF MEDICINE, NEW YORK, USA*

Type 2 immunity is involved in the regulation of metabolic homeostasis but is disrupted during obesity, promoting chronic low-grade inflammation. Helminth parasites are the strongest natural inducers of type 2 immunity and we previously reported that both infection with *Schistosoma mansoni* and treatment with a mixture of soluble egg antigens (SEA) improved whole-body metabolic homeostasis in insulin-resistant obese mice. Omega-1, a glycoprotein present in SEA, has previously been shown to trigger dendritic cell-mediated Th2 polarization by a glycan-dependent mechanism. In the present study, we investigated the effects of two plant-produced glycosylation variants of omega-1 on whole-body metabolic homeostasis. We showed that treatment with both recombinant omega-1 variants decreased fat mass and improved whole-body metabolic homeostasis in obese mice, an effect associated with increased adipose tissue Th2 cells, eosinophils and alternatively-activated macrophages. In the liver, omega-1 did not affect hepatic steatosis but increased IL-13-expressing Th2 cells and fibrotic gene markers. Remarkably, although the Th2-mediated immune response was abolished, the metabolic effects of omega-1 were still observed in obese $STAT6^{-/-}$ mice. By contrast, omega-1-induced liver fibrosis was significantly decreased. Omega-1 was found to inhibit food intake in both WT and $STAT6^{-/-}$ mice, without affecting locomotor activity or energy expenditure. Pair-feeding experiments showed that this reduction in food intake mediated most of the beneficial effects of omega-1. Altogether, we conclude that the improvement of metabolic homeostasis by omega-1 is independent of its Th2-inducing capacity and may be explained by brain-mediated inhibition of food intake and/or immune-independent direct interaction of omega-1 with metabolic cells.

Helminth-induced IL-4 expands bystander memory CD8$^+$ T cells for early control of viral infection

MARION ROLOT[1, ¶], ANNETTE M. DOUGALL[1, ¶], ALISHA CHETTY[2], JUSTINE JAVAUX[1], TING CHEN[1], XUE XIAO[1], BÉNÉDICTE MACHIELS[1], MURRAY E. SELKIRK[3], RICK M. MAIZELS[4], CORNELIS HOKKE[5], OLIVIER DENIS[6], FRANK BROMBACHER[2], ALAIN VANDERPLASSCHEN[1], LAURENT GILLET[1], WILLIAM G. HORSNELL[2], **BENJAMIN G. DEWALS[1]** (¶ CONTRIBUTED EQUALLY)

[1]IMMUNOLOGY-VACCINOLOGY, UNIVERSITY OF LIÈGE, LIÈGE, BELGIUM. [2]INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE AND DIVISION OF IMMUNOLOGY, UNIVERSITY OF CAPE TOWN, SOUTH AFRICA. [3]DEPARTMENT OF LIFE SCIENCES, IMPERIAL COLLEGE LONDON, LONDON, UK. [4]WELLCOME CENTRE FOR MOLECULAR PARASITOLOGY, INSTITUTE OF INFECTION, IMMUNITY AND INFLAMMATION, UNIVERSITY OF GLASGOW, GLASGOW, UK. [5]DEPARTMENT OF PARASITOLOGY, LEIDEN UNIVERSITY MEDICAL CENTER, LEIDEN, THE NETHERLANDS. [6]SCIENTIFIC INSTITUTE OF PUBLIC HEALTH, IMMUNOLOGY, BRUSSELS, BELGIUM.

Infection with parasitic helminths can imprint the immune system to modulate bystander inflammatory processes. Bystander or virtual memory CD8$^+$ T cells (T_{VM}) are non-conventional T cells displaying memory properties that can be generated through responsiveness to interleukin (IL)-4. However, it is not clear if helminth-induced type 2 immunity functionally affects the T_{VM} compartment. Here, we show that helminths expand CD44^{hi}CD62L^{hi}CXCR3^{hi}CD49d^{lo} T_{VM} cells through direct IL-4 signaling in CD8$^+$ T cells. Importantly, helminth-mediated conditioning of T_{VM} cells provided enhanced control of acute respiratory infection with the murid gammaherpesvirus 4 (MuHV-4). This enhanced control of MuHV-4 infection could further be explained by an increase in antigen-specific CD8$^+$ T cell effector responses in the lung and was directly dependent on IL-4 signaling. These results demonstrate that IL-4 during helminth infection can non-specifically condition CD8$^+$ T cells, leading to a subsequently raised antigen-specific CD8$^+$ T cell activation that enhanced control of viral infection.

A new risk factor for cancer – how helminth exposure influences colorectal cancer development.

BRUNETTE KATSANDEGWAZA[1], BRITTANY-AMBER JACOBS[1], **KATHERINE SMITH[1,2]**

[1] *UNIVERSITY OF CAPE TOWN, SOUTH AFRICA* [2]*CARDIFF UNIVERSITY, UK*

Colorectal cancer (CRC) is the third most prevalent cancer in the world and is set to increase by 94% in low and middle-income countries (LMIC) from 623,735 in 2012 to 1,212,861 cases by 2035. In these LMIC, risk factors such as diet change and infectious disease (including helminth infection) are thought to be the drivers in an anticipated exponential increase in CRC. Recently, myself and other researchers have found that infection with the gastrointestinal helminth *H. polygyrus* can exacerbate colitis-associated CRC. Critically, a diet rich in the essential fatty acid linoleic acid further exacerbated disease, resulting in increased pathology and tumour formation in infected mice. Active infection aggravated disease, as anthelminthic removal of live adult worms resulted in a significant improvement in CRC. *H. polygyrus* exacerbation of CRC was associated with significant alterations in typical anti-tumour responses, including reduced IFN-γ production by $CD4^+$ and $CD8^+$ T cells, increased IL-22 production by $CD4^+$ T cells and an increased number of innate cells, including macrophages, neutrophils and eosinophils in the peritoneal lavage. Helminth infection also resulted in increased inflammation in the spleen during initiation of CRC, which we associated with increased translocation of pathogenic gut microbiota to that site. Despite a defined role for alternate activation of macrophages in exacerbating CRC, our use of IL-4Rα$^{-/-}$ mice uncovered an unanticipated role for helminth-activated macrophages and eosinophils in limiting the pathology associated with CRC. Inhibition of the fatty acid metabolism pathway responsible for breakdown of linoleic acid into lipid inflammatory mediators using the COX-2 inhibitor celecoxib during helminth infection, significantly improved survival, reduced pathology and reduced tumour burden associated with helminth-induced CRC. This work demonstrates that both diet and helminth infection control CRC through a central fatty-acid metabolism pathway and provides candidates for immune-therapy to limit the anticipated escalation of CRC in LMIC.

Developing of a prophylactic vaccine to accelerate onchocerciasis elimination

SARA LUSTIGMAN[1], THOMAS R KLEI[2], PETER HOTEZ[3], BIN ZHAN[3], MARIA ELENA BOTTAZZI[3] AND DAVID ABRAHAM[4]

[1]LINDSLEY F KIMBALL RESEARCH INSTITUTE, NEW YORK BLOOD CENTER, NEW YORK, NY, USA; [3]DEPARTMENT OF PATHOBIOLOGICAL SCIENCES, SCHOOL OF VETERINARY MEDICINE, LOUISIANA STATE UNIVERSITY, BATON ROUGE, LA, USA; [3]TEXAS CHILDREN'S HOSPITAL CENTER FOR VACCINE DEVELOPMENT, DEPARTMENT OF PEDIATRIC TROPICAL MEDICINE, NATIONAL SCHOOL OF TROPICAL MEDICINE, BAYLOR COLLEGE OF MEDICINE, HOUSTON, TX, USA; AND [4]DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY, SIDNEY KIMMEL MEDICAL COLLEGE, THOMAS JEFFERSON UNIVERSITY, PHILADELPHIA, PA, USA.

Human onchocerciasis—commonly known as river blindness—is one of the most devastating yet neglected tropical diseases, leaving many millions in Sub-Saharan Africa blind and/or with chronic disabilities. Attempts to eliminate onchocerciasis, primarily through the mass drug administration of ivermectin remains challenging and has been heightened by the recent news that drug-resistant parasites are developing in some populations after years of drug treatment. Needed, and needed now, in the fight to eliminate onchocerciasis are new tools, such as preventive and therapeutic vaccines to "complement" the present control measures. We will present the progress we have made to advance the onchocerciasis vaccine from the research lab into the clinic. Using a robust down selection screening process we have identified two *O. volvulus* vaccine candidates, Ov-103 and Ov-RAL-2, and their *Brugia malayi* homologues as the most promising candidates. Both proteins induced protection individually or as a bivalent vaccine (co-administration or as a fusion protein) when formulated with alum using small animal models. The mechanism of protective immunity induced in mice by the adjuvanted Ov-103 and Ov-RAL-2 vaccines appear to be multifactorial with roles for cytokines, chemokines, antibody and specific effector cells. Using human mono-specific Ov-103 and Ov-RAL-2 antibodies we were able to inhibit 70-80% of molting of *O. volvulus* L3 larvae *in vitro* (but did not kill) when cultured in the presence of naïve human monocytes suggesting that monocytes and their soluble factors might be associated with protective immunity also in humans. The critical path to the development of an *O. volvulus* prophylactic vaccine will be also discussed.

Structural and immunological approach to ASP-based vaccine development against cattle parasites *Ostertagia ostertagi* and *Cooperia oncophora*

JIMMY BORLOO[1], IRIS PEELAERS[1], EDWIN CLAEREBOUT[1], PETER GELDHOF[1]

[1] *LABORATORY OF PARASITOLOGY, FACULTY OF VETERINARY MEDICINE, GHENT UNIVERSITY, MERELBEKE, BELGIUM*

Endogenous *Ostertagia ostertagi* and *Cooperia oncophora* activation-associated secreted proteins (ASP) have previously been described in yielding protection when administered as a vaccine to cattle in experimental studies, whereas *Pichia*-produced versions of these ASPs failed to protect against either *O. ostertagi* or *C. oncophora* challenge infections. We have taken up the effort of biochemically comparing the endogenous molecules to their recombinant equivalent and found that: i) multiple sequence polymorphisms occur in endogenous ASPs, ii) *N*-glycan profiles substantially differ between endogenous *versus* recombinant ASPs, and iii) aberrant disulfide bonding occurs in endogenous *O. ostertagi* ASP and recombinant *C. oncophora* ASP. In terms of immune response, we noted that removal of the *N*-glycans from the endogenous *C. oncophora* ASP lowers antibody recognition, whereas the opposite effect was found when cleaving off the *Pichia N*-glycans, illustrating that the endogenous *N*-glycan may be part of a crucial epitope. On the other hand, the loss of tertiary structure in *O. ostertagi* ASP also resulted in lowered IgG titers, demonstrating the importance of protein structure in eliciting a proper immune response. Further fine-tuning of ASP glycosylation and disulfide bonding, combined with epitope mapping, is ongoing. We are applying all gathered knowledge in the production of new recombinant versions of both *O. ostertagi* and *C. oncophora* ASPs with the ultimate goal that these yield protection levels in cattle rivalling (or surpassing) those of their endogenous counterparts.

Determining anti-glycan antibody responses to *Haemonchus contortus* Barbervax vaccine using glycan microarray screening.

EVE HANKS[1], ANGELA VAN DIEPEN[2], DAVID SMITH[3], GEORGE FJ NEWLANDS[3], STEWART BURGESS[3], DAVID P KNOX[3], ALASDAIR J NISBET[3], TOM N MCNEILLY[3], CORNELIS H HOKKE[2], COLLETTE BRITTON[1]

[1]INSTITUTE OF BIODIVERSITY, ANIMAL HEALTH AND COMPARATIVE MEDICINE, UNIVERSITY OF GLASGOW, UK, [2]LEIDEN UNIVERSITY MEDICAL CENTER, DEPARTMENT OF PARASITOLOGY, LEIDEN, NETHERLANDS AND [3]MOREDUN RESEARCH INSTITUTE, PENICUIK, EDINBURGH, UK

Haemonchus contortus is a highly pathogenic, blood feeding gastrointestinal nematode of small ruminants. High levels of protective immunity can be achieved against challenge infection by vaccinating sheep with the native *H. contortus* gut glycoprotein vaccine Barbervax. Previous studies have shown that vaccination induces high antibody titres to two main glycoproteins present in Barbervax, aminopeptidase H11 and the H-gal-GP complex. Approximately 90% of the antibody reactivity is targeted towards glycan components of these glycoproteins. To identify the specific glycan structures recognised by host antibody following vaccination, glycan array screening was carried out. Arrays were printed with enzymatically released Barbervax N-glycans fractionated by HPLC and screened with serum from 56 vaccinated lambs, predominantly from field trials carried out in Australia. These lambs all showed high levels of anti-Barbervax IgG based on ELISA titre at peak *H. contortus* challenge. From the serum recognition profiles, we identified a number of glycans that were recognised consistently by serum from these lambs. We examined any relationships between level of IgG binding to specific glycan fractions and three measures of protection to *H. contortus* infection: mean faecal egg count, change in haemoglobin level during the trials and antibody titre at peak challenge. We identified a small number of Barbervax glycan fractions, the recognition of which correlated significantly with protection. Several synthetic di-, tri- and tetrasaccharides were also included on the arrays and synthetic LDNF was strongly recognised by some of this cohort. Further work is underway to determine the structures of the immunogenic Barbervax glycans and to examine whether specific glycans of interest may be involved in inducing immunity. This is important in identifying the mechanisms of vaccine-induced protection to *H. contortus* and in development of a future synthetic vaccine.

Extracellular vesicle vaccines for immunity to helminths

GILLIAN COAKLEY[1,2], AMY BUCK[1] , **RICK MAIZELS**[2]

[1] INSTITUTE OF IMMUNOLOGY AND INFECTION, UNIVERSITY OF EDINBURGH, UK; [2] WELLCOME CENTRE FOR MOLECULAR PARASITOLOGY, INSTITUTE FOR INFECTION, IMMUNITY AND IFLAMMATION, UNIVERSITY OF GLASGOW, UK.

We originally showed that the murine parasite *Heligmosomoides polygyrus* releases abundant quantities of extracellular vesicles, which contain a specific population of protein and RNA molecules. These vesicles can fuse with and deliver their cargo to host cells; in the case of macrophages, vesicles inhibit the alternative activation required to mount protective immunity to parasite infection. We have found that host antibodies reactive with the vesicles redirect them into the lysosomal degradative pathway, preventing immune interference and rescuing alternative activation. Moreover, the vesicles themselves can, when presented in adjuvant, act as a vaccine in generating protective immunity against challenge infection with *H. polygyrus*. The implications of this new strategy for helminth vaccine development will be discussed.

POSTER SESSION 1

ABSTRACTS

1. Foxp3$^+$ regulatory T cells require IL-4Rα signaling to control helminth-induced lung emphysema

NADA ABDEL AZIZ[1,2,3,4], THABO MPOTJE[1,2,3], JUSTIN KOMGUEP NONO[1,2,3,5 #], AND FRANK BROMBACHER[1,2,3 #]

[1]INTERNATIONAL CENTRE FOR GENETIC ENGINEERING AND BIOTECHNOLOGY (ICGEB), CAPE TOWN, SOUTH AFRICA; [2]DIVISION OF IMMUNOLOGY, HEALTH SCIENCE FACULTY, UNIVERSITY OF CAPE TOWN; [3]IMMUNOLOGY OF INFECTIOUS DISEASE RESEARCH UNIT, SOUTH AFRICAN MEDICAL RESEARCH COUNCIL (SAMRC), CAPE TOWN; [4]BIOTECHNOLOGY/BIOMOLECULAR CHEMISTRY PROGRAM, CHEMISTRY DEPARTMENT, CAIRO UNIVERSITY, EGYPT; [5]INSTITUTE OF MEDICAL RESEARCH AND MEDICINAL PLANT STUDIES (IMPM), MINISTRY OF SCIENTIFIC RESEARCH AND INNOVATION, YAOUNDÉ. CAMEROON. #CO-CORRESPONDING AUTHORS.

Helminth-induced type 2 (Th2) immune responses play a crucial role in conferring a protection to the host, in terms of worm expulsion, although, however the mechanism(s) by which type 2 immunity control tissue damage induced by helminth migration through vital tissues remain poorly understood. Emphysema is one of the most devastating pathology, induced by parasite migration, which causes a reduction in lung function and difficulty in breathing. Emphysema gets worse over time and continues even after the parasite has left the lung. The mechanism(s) underlying the host protection or susceptibility to emphysema is yet to be defined. To interrogate the regulation of helminth-induced emphysema, we used a *Nippostrongylus brasiliensis* model whereby mice were infected with 500 L3 larvae and emphysema was evaluated 9 days post-infection. Using an inducible model of IL-4Rα global deletion (Rosa-CreER$^{T2-/+}$ IL-4Rα$^{-/lox}$) we found that removal of IL-4Rα 5-days post infection results in worsened emphysema compared to infected littermate controls. The data recapitulated with published reports showing an important role of IL-4Rα signaling in mediating acute wound healing during *N. brasiliensis* infection. Further investigations on IL-4Rα responsiveness cells in the lung have aided in the identification of Foxp3$^+$ Treg cells as a key component in the regulation of emphysema in our model. In fact, specific deletion of IL-4Rα on Foxp3$^+$ Treg cells (Foxp3^{cre} IL-4Rα$^{-/lox}$ mice) led to heavier mucus production and exacerbated helminth-induced emphysema 9 days post-infection. Mechanistically, deletion of IL-4Rα on Foxp3$^+$ Treg population resulted in impairment of Foxp3$^+$ Treg cells recruitment to the inner layer of the alveoli of the lungs during *N. brasiliensis* infection. Taken together, our findings indicate that IL-4Rα-mediated signaling on Foxp3$^+$ Treg cells, in particular, is crucial in protecting the host against helminth-induced emphysema.

2. A flexible molecular diagnostic method for the diagnosis of *Fasciola* spp. in ruminant faecal samples

NICHOLA E D CALVANI, P A WINDSOR, R D BUSH AND J ŠLAPETA

SYDNEY SCHOOL OF VETERINARY SCIENCE, FACULTY OF SCIENCE, THE UNIVERSITY OF SYDNEY, CAMPERDOWN, NSW, AUSTRALIA

Fasciolosis is a re-emerging zoonotic disease of ruminants with worldwide importance. Commonly-employed diagnostic methods for *Fasciola* spp., such as a traditional sedimentation and faecal egg count, or a commercially-available coprological ELISA, have limitations in their sensitivity or ability to differentiate species. A reliable DNA isolation method coupled with real-time PCR has the potential to address these issues by providing highly-sensitive and quantitative molecular diagnosis from faecal samples. A molecular diagnostic workflow for the sensitive detection and species differentiation of *Fasciola* spp. in cattle and sheep faecal samples was developed. Two methods of sample preparation (concentrated vs. raw) and egg disruption (disruption in a high-speed benchtop homogeniser vs disruption in a standard benchtop vortex) were compared. Concentration of faecal samples via a traditional sedimentation resulted in an analytical sensitivity of ≤1 egg per gram (EPG) in both sheep and cattle. DNA isolation from raw samples yielded a positive threshold of 10 and 20 EPG for sheep and cattle, respectively. The result is a flexible diagnostic workflow capable of adaptation to laboratories with varying diagnostic needs and resources.

3. Investigating acetylcholinesterases in *Taenia crassiceps* larvae and their excretory/secretory products, and the ability of these to functionally effect neuronal electrophysiology

ANJA DE LANGE AND J.V. RAIMONDO

DEPARTMENT OF HUMAN BIOLOGY, UNIVERSITY OF CAPE TOWN FACULTY OF HEALTH SCIENCES, ANZIO ROAD, CAPE TOWN, 7935, SOUTH AFRICA.

Neurocysticercosis (NCC) is a medical condition in humans where larvae of the cestode *Taenia solium* infect the nervous system. Seizures are the most common symptom of NCC and affect millions of people worldwide. Although the onset of symptoms in NCC appears linked to the death of larvae, the mechanisms underlying seizures remain unknown. To evade the immune system many nematodes and cestodes secrete acetylcholinesterases. Acetylcholine is a well characterized neurotransmitter and as such we chose to investigate whether *Taenia* larvae produce acetylcholinesterases (AChEs), and whether these can functionally affect neurons. *Taenia crassiceps* larvae were cultured and their excretory/secretory (E/S) products collected and concentrated. Larvae were then homogenized in PBS, centrifuged, and the supernatant retained. The presence of AChEs in Taenia products was determined using Ellman's assays. Inhibition with the AChE inhibitor BW284c51 was assessed. Staining for AChEs was performed on whole larval mounts, larval sections and on non-denaturing PAGE gels of Taenia products. The ability of the Taenia AChEs to functionally effect neurons was assessed by applying acetylcholine to neurons in the absence- and presence of *Taenia crassiceps* products on a patch clamp rig. Moderate acetylcholinesterase activity is reported in *Taenia crassiceps* E/S products and homogenate in comparison to *Heligmosomoides polygyrus* E/S products, which were utilized at a positive control. Inhibition of *Taenia crassiceps* AChEs with BW284c51 displayed a dose effect, in contrast to *Heligmosomoides polygyrus* AChEs which were strongly inhibited by low a concentration of BW284c51. Staining revealed that AChEs appear to be present within the larval tegument, as well as at the tegument surface, and that *Taenia crassiceps* E/S products appear to contain only one acetylcholinesterase, whilst the Taenia homogenate appears to contain two. We show that *Taenia* larvae produce AChEs that may functionally effect brain activity in NCC.

4. Using simulated hypoxia in *C. elegans* as a platform for anthelmintic drug discovery

SAMANTHA DEL BORRELLO, MARGOT J. LAUTENS, KATHLEEN DOUCET, MARK SPENSLEY, MICHAEL SCHERTZBERG, AMY A. CAUDY, ANDREW G. FRASER

TERRENCE DONNELLY CENTRE FOR CELLULAR AND BIOMOLECULAR RESEARCH, DEPARTMENT OF MOLECULAR GENETICS, UNIVERSITY OF TORONTO, CANADA

Parasitic helminth infections affect ¼ of the world, and result in thousands of deaths every year as well as economic losses in agriculture. This is in part due to increasing anthelmintic resistance, thus fueling a need for the discovery of novel anthelmintics. During host infection, parasitic helminths are in an oxygen-deprived environment, during which they use special forms of anaerobic respiration to survive. We established an image-based assay of worm movement—the acute assay—and found that worms treated with potassium cyanide (KCN) become paralyzed, however additional treatment with 2-Deoxy-D-glucose (2DG) recovers movement. KCN prevents oxidative phosphorylation in the aerobic electron transport chain (ETC), and 2DG is a glucose analog that blocks glycolysis. A key question is how worms are producing ATP when both glycolysis and the ETC are blocked. We used RNAseq to investigate the transcriptional response to KCN + 2DG, and found our treatment activates the hypoxia response. Mutant analysis of genes required for this response has shown this response is required for recovery. Interestingly, we also see this phenotype upon inhibition of Complex I with rotenone. Therefore, we conclude that recovery from paralysis requires at least two processes: a working hypoxia response, and the anaerobic electron transport chain. My project goal is to better understand these and other anaerobic pathways to uncover new anthelmintic targets. Another aim is to screen for compounds that inhibit recovery. To date, we have screened multiple libraries and have found hits specific to our platform. We look to further investigate the processes involved in recovery as well as our hits from drug screening using forward genetic screens.

5. Venus Kinase Receptors in the flatworm *Macrostomum lignano*

JÉRÔME VICOGNE[1], STIJN MOUTON[2], ALEXANDRA MOUGEL[1], STÉPHANIE CABY[1], MARIE-JOSÉ GHORIS[1], RAYMOND PIERCE[1], EUGENE BEREZIKOV[2], OLEG MELNYK[1], **COLETTE DISSOUS**[1]

[1]- CBF TEAM, CIIL, INSTITUT DE BIOLOGIE DE LILLE, INSERM U1019- CNRS UMR8204, INSTITUT PASTEUR DE LILLE, 59021 LILLE, FRANCE [2]- ERIBA, UNIVERSITY OF GRONINGEN, UNIVERSITY MEDICAL CENTER GRONINGEN, 9713 AV GRONINGEN, THE NETHERLANDS

Venus Kinase Receptors (VKRs) are atypical Receptor Tyrosine Kinases present only in invertebrates. They are composed of Venus Flytrap extracellular modules linked to tyrosine kinase domains similar to those of insulin receptors. VKRs are activated by amino-acids and specially by L-arginine. VKRs are found in diverse invertebrate phyla and particularly in Platyhelminthes. They were discovered for the first time in the parasitic flatworm *Schistosoma mansoni* (Vicogne et al, 2003) and their importance in the reproduction of this parasite has been described (Vanderstraete et al, 2014). Further work is needed to elucidate the physiological function of the VKRs in flatworms. However, in spite of the considerable efforts made to develop molecular tools efficient for studying schistosome biology, the complex parasite life cycle represents a major brake to reverse genetics and in-depth fundamental studies. The free-living flatworm *Macrostomum lignano* appears as an attractive and alternative model to fill this gap, since it offers a large panel of molecular tools (including stem cell tracking, RNAi and whole-mount *in situ* hybridization) and has also a high regeneration capacity facilitated by neoblasts. From genome sequencing and annotation (www.macgenome.org), four different VKR genes (*Mlvkr 1-4*) were identified in *M. lignano* and their expression in the worm was deduced from positional RNA-Seq data (Arbore et al, 2015). We will present the structure of the four MlVKR 1-4 proteins, the phylogeny of VKRs in flatworms including *S. mansoni* and the planaria *Schmidtea mediterranea* in which two (SmVKR1 and SmVKR2) and three (SmedVKR1-3) VKR genes are respectively expressed. Preliminary RNA interference results confirmed the potential importance of MlVKR receptors in sexual maturation and gametogenesis of *M. lignano.*

6. Evolutionary and structural divergence of genes involved in the small RNA pathways of platyhelminthes

SANTIAGO FONTENLA, JOSE TORT

DEPARTAMENTO DE GENETICA, FACULTAD DE MEDICINA, UNIVERSIDAD DE LA REPUBLICA, URUGUAY

Small RNAs are relevant post-transcriptional regulators of gene expression in many biological processes as development and cell differentiation. Recently, we improved the knowledge on the conservation of small RNA pathways in Platyhelminthes by analyzing an extended set of Neodermatan species, and the Turbellarians *M. lignano* and *S. mediterranea*. In the present work, we included seven additional Turbellarian transcriptomes in our analysis pipeline, that comprehend species ranging from the most ancestral platyhelminthes to the closest free-living clade of the Neodermatans. We observed that while small RNA pathways seem to be functional in all platyhelminthes there is a gradual simplification. For example, the RNA dependent RNA polymerases, which are involved in the amplification of the silencing response, are only conserved in some of the most ancestral flatworms. On the other hand, the PIWI argonautes that are essential in the silencing of transposable elements are conserved in all Turbellarians. Interestingly they group in two clusters, one of them composed by Turbellarian genes and orthologs from other metazoan, and the second one composed exclusively by Turbellarian species. We, also, found that while flatworm PIWIs conserve PAZ/PIWI, conservation of other domains is more variable. In addition to PIWI, we detected another two subfamilies of Argonautes genes, the Ago-like, orthologous to canonical Ago, and the FL-AGOs, a unique novelty acquired in the root of Platyhelminthes. We used Argonaute alignments to study sequence conservation between the three subfamilies, finding that Ago-like subfamily conservation is high throughout the evolution of metazoans, conservation on the other two subfamilies is lower, being the lowest in the PIWI cluster. Finally, using most conserved amino acidic residues and relevant motifs from functional domains, we developed a classification method, which will probe to be useful for the classification of Argonautes not only from flatworms but also from other metazoan species.

7. Fatty acid binding proteins (FABP) of parasitic cestodes: functional studies and evaluation as novel therapeutic targets

JULIÁN BÉLGAMO[1], JORGE PÓRFIDO[1#a], URIEL KOZIOL[2], ESTELA CASTILLO[2], MICHAELA HERZ[3], MATÍAS PEREZ[4], MARA ROSENZVIT[4], KLAUS BREHM[3], BETINA CORSICO[1] AND **GISELA FRANCHINI**[1].

[1] INIBIOLP-CONICET, FAC.DE CIENCIAS MÉDICAS, UNIVERSIDAD DE LA PLATA, ARGENTINA [2] SECCIÓN BIOQUÍMICA, FACULTAD DE CIENCIAS, UNIVERSIDAD DE LA REPÚBLICA, URUGUAY [3] INSTITUT FÜR HYGIENE UND MIKROBIOLOGIE, UNIVERSITÄT WÜRZBURG, GERMANY [4] IMPAM-CONICET, FACULTAD DE MEDICINA, UNIVERSIDAD DE BUENOS AIRES, ARGENTINA [#a] CURRENT ADDRESS: INSTITUT PASTEUR MONTEVIDEO, URUGUAY.

The analysis of the genome and transcriptome of *Echinococcus granulosus* and *E. multilocularis,* causative agents of hydatid disease, suggests a high expression of lipid-binding proteins, including proteins that bind fatty acids (FABPs), which may participate in the uptake of host lipids for energy metabolism, membrane construction, and lipid-based signalling, the latter possibly also encompassing modification of the host's immune and inflammatory defence systems. The aim of this work is to identify FABPs in the genome of *E. granulosus* and *E. multilocularis*, characterise their function and to evaluate them as potential new targets for chemotherapy. We predicted five FABP isoforms in *E. multilocularis*, that were cloned and sequenced and are now being purified recombinantly for *in vitro* studies. The isoforms tested for ligand binding show an affinity comparable to the mammalian counterparts. In addition, transcriptomic data from several sources showed differential expression patterns of FABPs at different stages of the life cycle of *E. multilocularis* being EmFABP1 the most highly expressed FABP in this organism. Whole mount in situ hybridization samples also revealed that EmFABP1 is present in tegumental cells from vesicles and from the distal part of protoscoleces. In this sense other EmFABPs are under study. Regarding, the analysis of cestode FABPs as novel therapeutic targets, *in vitro* binding of an inhibitor of mammalian FABPs (HTS01037) was assessed by fluorescence methodologies. Preliminary results indicate that HTS01037 binds to cestode FABPs with lower affinities than mammalian. Additionally, using an *in vivo* cysticercosis (*T. crassiceps*) model we evaluated the effect of HTS01037 on *T. crassiceps* cisticerci. Altogether, these results suggest that FABP isoforms may play specific roles in different stages/tissues, related to lipid metabolism of parasites and might be good therapeutic targets.

8. Characterization of the major pseudocoelomic proteins of the giant kidney worm, *Dioctophyme renale*

NAHILI GIORELLO[1, 4], DANIELA PEDRASSANI[2], MARCOS ANDRÉ [3], ROSANGELA ZACARIAS MACHADO[3], MARCOS BUTTI[4], NILDA A. RADMAN[4], MALCOLM W. KENNEDY[5], BETINA CÓRSICO[1] AND GISELA FRANCHINI[1].

[1] INIBIOLP-CONICET, FAC.DE CIENCIAS MÉDICAS, UNIVERSIDAD DE LA PLATA, ARGENTINA [2]DEPARTAMENTO DE MEDICINA VETERINÁRIA, UNIVERSIDADE DO CONTESTADO - UNC, CANOINHAS, SC, BRASIL [3]DEPARTAMENTO DE PATOLOGIA VETERINÁRIA, UNIVERSIDADE ESTADUAL PAULISTA - UNESP, JABOTICABAL, SP, BRASIL [4] LABORATORIO DE PARASITOSIS HUMANAS Y ZOONOSIS PARASITARIAS, FAC. DE VETERINARIA, UNIVERSIDAD DE LA PLATA, [4] INSTITUTE OF BIODIVERSITY, ANIMAL HEALTH AND COMPARATIVE MEDICINE, UNIVERSITY OF GLASGOW UK

Dioctophyma renale, commonly known as the giant kidney worm develops in, and completely destroys mammalian kidneys, and is thereby a debilitating and potentially lethal parasite of humans, domestic animals and endangered wildlife. Despite the importance and threat for humans of this parasitic disease there is little information about the molecular bases of this organism (e.g. genome and proteome). Among domestic animals it is particularly pathogenic and common in dogs that live close to rivers and the infection is diagnosed only by urine analysis, ultrasonography, surgery, or at necropsy. Moreover, although the parasite is usually located in one of the kidneys, worms may also develop to adulthood in sites other than these organs, such as the abdominal cavity, subcutaneous tissues, etc. Given this, current diagnostic methods are of poor sensitivity, frequently giving false negative results. In this regard, recently published data show the existence of soluble antigens from the esophagus of *D. renale* may help to determine infections in dogs. Our work is aimed at discovering specific proteins from *D. renale* that might be useful as new diagnostic markers for their use in dogs and potentially in humans. So far, we characterised the soluble proteins of pseudocelomic fluid (PCF) of adult parasites. Two proteins, P17 and P44, dominate the PCF of both male and females. P17 is of 16,622 Da by mass spectrometry, and accounts for the intense red colour of the adult parasites. It may function to carry or scavenge oxygen and be related to the 'nemoglobins' found in other nematode clades. P44 is of 44,460 Da and was found to associate with fatty acids. Both proteins were studied by immunoassays in comparison with esophagus proteins to test their potential as diagnostic markers. Interestingly, while P44 was found to be immunogenic in the dog sampled, P17 was not.

9. WormBase ParaSite - 2018 update

KEVIN L. HOWE[1], WOJTEK BAZANT[2], TUAN LE[1], FAYE RODGERS[2], MATTHEW BERRIMAN[2]

[1]EMBL EUROPEAN BIOINFORMATICS INSTITUTE & [2]WELLCOME SANGER INSTITUTE, CAMBRIDGE, UK

WormBase ParaSite (http://parasite.wormbase.org) is a comprehensive effort to integrate, organise and present data for all nematode and platyhelminth genomes. Four years on from the start of the project, we now include genome data for over 100 species, adding value by way of systematic and consistent functional annotation (e.g. protein domains and Gene Ontology terms), gene expression analysis (e.g. alignment of life-stage specific RNASeq sets), and comparative analysis (e.g. orthologues and paralogues). We provide several ways to explore the data, including genome and gene summary pages, text search, sequence search, a query wizard, bulk downloads, a choice of genome browsers, and a programmatic interface. We will present the core features of WormBase ParaSite, with a focus on new data and recent improvements to functionality. We will also present our plans for the next major phase of development of the project, including an enriched suite of tools for exploring gene expression. As ever, we encourage the community to describe your use-cases and make suggestions for improvements to help us prioritise future work.

10. Cancer cell behaviour following parasite exposure

BRITTANY-AMBER JACOBS[1], ALISHA CHETTY[1], BRUNETTE KATSANDEGWAZA[1], WILLIAM HORSNELL[1], GEORGIA SCHÄFER[2], SHARON PRINCE[3] AND KATHERINE A SMITH[1, 4]

[1] DEPARTMENT OF PATHOLOGY, DIVISION OF IMMUNOLOGY, UNIVERSITY OF CAPE TOWN, SOUTH AFRICA [2] DEPARTMENT OF INTEGRATIVE BIOMEDICAL SCIENCES, INSTITUTE FOR INFECTIOUS DISEASE AND MOLECULAR MEDICINE, UNIVERSITY OF CAPE TOWN; [3] DEPARTMENT OF HUMAN BIOLOGY, DIVISION OF CELL BIOLOGY, UNIVERSITY OF CAPE TOWN; [4] SCHOOL OF MEDICINE, INSTITUTE OF INFECTION AND IMMUNITY, CARDIFF UNIVERSITY,UK

Infectious diseases, including helminth parasites, are estimated to cause 33% of the cancer cases in sub-Saharan Africa. While certain helminths are conclusive biological carcinogens, others have been shown to modulate inflammatory diseases, including cancer. It is currently unknown why differing helminth infections promote or prevent cancer development, or which cellular mechanisms are altered following exposure to helminths. Using several *in vitro* assays and *in vivo* models this study aimed to determine the effect that antigens derived from certain helminths have on cervical and colorectal cancer behaviour. Through these techniques, it was revealed that *Nippostrongylus brasiliensis* L3 antigen significantly decreased cervical cancer cell migration and the expression of markers associated with cancer cell metastasis, vimentin and N-cadherin *in vitro*. Expression of vimentin was also significantly reduced in the murine female genital tract following *N. brasiliensis* infection. In addition, *N. brasiliensis* L3 significantly decreased the expression of cell-surface vimentin, a known restriction factor for the cancer-causing virus Human Papillomavirus (HPV), while unexpectedly resulting in a significant decrease in HPV16 pseudovirion internalisation. Furthermore, *in vitro* exposure of a murine and human colorectal cancer cell line to *Heligmosomoides polygyrus* antigen and its excretory-secretory (ES) product significantly decreased cell proliferation with an accompanied increase in the expression of the cell-cycle regulator proteins p21 and p53. This work generates the novel and fascinating hypothesis that helminth products can inhibit cancer progression through regulation of cancer cell metastasis marker expression and cell-cycle regulator protein expression. These findings have important implications for cancer patients in helminth endemic areas.

11. Helminths and Colitis: Friends or Foes?

BRUNETTE KATSANDEGWAZA[1], BRITTANY AMBER JACOBS[1], ALISHA CHETTY[1], WILLIAM HORSNELL[1], KATHERINE SMITH[1,2]

1.INSTITUTE OF INFECTIOUS DISEASE AND MOLECULAR MEDICINE, UNIVERSITY OF CAPE TOWN; 2.CARDIFF UNIVERSITY, CARDIFF, UK.

The ability of helminths to regulate bystander inflammatory disorders and the mechanisms by which they carry this out are of great scientific interest. Currently, established literature emphasizes the protective role of helminth infection in mouse models of inflammatory bowel disease (IBD). Using the gastrointestinal helminth *Heligmosomoides polygyrus*, we demonstrate that helminth infection exacerbates IBD in 2 different models, namely the Oxazolone and DSS models. Exacerbation is diet, gender and *H. polygyrus* dose-dependent but is however independent of phase of infection, with both acute and chronic infections resulting in the same phenotype. Helminth infection results in increased colon inflammation, with the resultant splenomegaly positively correlating with neutrophilia. Exacerbation is characterised by significant bacterial translocation to the spleen, which is concluded to be a result of loss of intestinal epithelial integrity and a shift in bacterial composition as evidenced by gram staining. Administration of a probiotic during helminth infection reduces helminth exacerbation of DSS colitis, restores epithelial integrity and ameliorated splenomegaly. Our work uncovers an unexpected and novel role for live helminth infection in exacerbating IBD and suggests that helminth-induced dysbiosis of the microbiota may drive disease. These studies reveal restoration of the microbiota through probiotics or helminth eradication as potential therapies for the treatment of gastrointestinal inflammatory disorders.

POSTER SESSION 2

ABSTRACTS

12. Cathepsins L3 from parasitic flukes as therapeutic targets

ADRIAN LEONTOVYČ[1, 2], JAN DVOŘÁK[1, 3], ADÉLA JÍLKOVÁ[1], ANTHONY J. O'DONOGHUE[4], MARTIN HORN[1], CONOR R. CAFFREY[4], JOHN P. DALTON[5], MICHAEL MAREŠ[1]

[1]INSTITUTE OF ORGANIC CHEMISTRY AND BIOCHEMISTRY, CZECH ACADEMY OF SCIENCES, PRAGUE, CZECH REPUBLIC [2]FIRST FACULTY OF MEDICINE, CHARLES UNIVERSITY, PRAGUE; [3]DEPARTMENT OF ZOOLOGY AND FISHERIES, CZECH UNIVERSITY OF LIFE SCIENCES, PRAGUE; [4]CENTER FOR DISCOVERY AND INNOVATION IN PARASITIC DISEASES, SKAGGS SCHOOL OF PHARMACY AND PHARMACEUTICAL SCIENCES, UNIVERSITY OF CALIFORNIA SAN DIEGO, LA JOLLA, USA [5] SCHOOL OF BIOLOGICAL SCIENCES, MEDICAL BIOLOGY CENTRE, QUEEN'S UNIVERSITY BELFAST, BELFAST, NORTHERN IRELAND, UK

Proteolytic enzymes of parasites are attractive drug targets for antiparasitic therapy. Our work is focused on cathepsin L3 from two species of trematode helminths infecting humans. (1) The blood fluke *Schistosoma mansoni* is the major agent of schistosomiasis, the second most important parasitic infection after malaria with 250 million people infected worldwide and many more at risk. Cathepsin L3 is an important digestive enzyme degrading host blood proteins. (2) The liver fluke *Fasciola hepatica* is one of the most devastating parasites of livestock, which also infects humans. Annual economic loss caused by fasciolosis is estimated to reach 4 *billion* US $. Cathepsin L3 is a critical enzyme for invasion into definitive host; its collagenolytic activity enables penetration of intestine wall. Because of the crucial role of cathepsin L3, regulation of its function is a promising approach for suppression of the parasites. Recombinant enzymes were recombinantly expressed in *P. pastoris* expression system and functional properties of their active site were investigated using libraries of synthetic substrates. We initiated a high-throughput mapping of SmCL3 and FhCL3 inhibitor specificity using library of peptidomimetic inhibitors. This will be followed by crystallographic analysis of binding mode of the best inhibitors. 3D structure models will be employed for rational designing of specific inhibitors as potential drugs against schistosomiasis and fasciolosis.

13. Haemonchus contortus soluble extracts suppress NLRP3 inflammasome activation via the circRNA-miRNAs-mRNA axis

SI WANG, CHENRU FAN, XUN SUO, **XIANYONG LIU**

STATE KEY LABORATORY OF AGROBIOTECHNOLOGY, KEY LABORATORY OF ZOONOSIS OF MINISTRY OF AGRICULTURE, NATIONAL ANIMAL PROTOZOA LABORATORY AND COLLEGE OF VETERINARY MEDICINE, CHINA AGRICULTURAL UNIVERSITY, BEIJING, 100193, CHINA

The pyrin domain-containing 3 (NLRP3) inflammasome is an important cellular machinery that mounts inflammatory responses by processing and secretion of the pro-inflammatory cytokine interleukin-1β (IL-1β). Previous studies suggested that suppressing of NLRP3 inflammasome activation contributed to type 2 immunity, which are crucial to helminth infection. Here we show that *haemonchus contortus* soluble extracts (HcAg) suppress NLRP3 inflammasome activation through a circRNA-miRNAs-mRNA axis. Since the expression profile of NLRP3 is a critical checkpoint for NLRP3 inflammasome activation, we sequenced and computationally analyzed sheep fibroblast-like cell line RNA after HcAg stimulation. Interesting, HcAg stimulation significantly decreased the expression of circRNA_1599 (log_2Fold Change = -7.9977, padj = $2.3005E^{-12}$), which is the corresponding circular RNA of NLRP3 transcript. Low circRNA_1599 expression increases miRNAs activity by less circRNA-miRNA interaction and thus decreasing NLRP3 expression. Together, our data postulates a new mechanism that helminth modulate host immunity via a circRNA-miRNAs-mRNA axis.

14. Preliminary genomic analyses of a Brazillian isolate of *Haemonchus contortus* in a model for monepantel resistance

SIMONE NICIURA[1], ANA CLÁUDIA ALBUQUERQUE[2], GIOVANNA CRUVINEL[3], CAROLINE MORAES[4], ANA CAROLINA CHAGAS[1], SERGIO ESTEVES[1], MAGDA BENAVIDES[5], ALESSANDRO AMARANTE[2]

[1]*EMBRAPA PECUÁRIA SUDESTE, BRAZIL* [2]*INSTITUTO DE BIOCIÊNCIAS DE BOTUCATU, UNESP, BRAZIL* [3]*CENTRO UNIVERSITÁRIO CENTRAL PAULISTA, BRAZIL* [4]*UNIVERSIDADE FEDERAL DE SÃO CARLOS, BRAZIL* [5]*EMBRAPA PECUÁRIA SUL, BRAZIL*

Anthelmintic resistance is a worldwide problem in sheep production. Monepantel, the most recent anthelmintic released in market, has some reports of resistance, but it is still the most effective treatment to control gastrointestinal parasites. To study the molecular mechanisms of monepantel resistance before its establishment, we aimed to induce resistance in *Haemonchus contortus* infecting Santa Ines sheep using monepantel subdosing. After a 564-day trial, the highest monepantel dose that resulted in larval recovery was 0.75 mg/kg (30% of the recommended 2.5 mg/kg). Then, Santa Ines was not a suitable host breed to induce monepantel resistance in *H. contortus*, probably due to its reported immune resistance to parasites. Then, we used a field resistant isolate of *H. contortus* obtained from Ile de France sheep for backcrossing and introgression of resistance genes in a susceptible isolate. Pools of 30,000 L3 from the parental resistant and from F2 population were submitted to DNA extraction, library preparation and Illumina 150-bp paired-end sequencing to generate about 37G of data for each one of 6 samples. Sequence mapping rates to *H. contortus* reference genome ranged from 54.95 to 55.49% in McMaster strain (BioProject PRJNA205202), an Australian isolate, and from 79.12 to 79.43% in HMco3 strain (BioProject PRJEB506), an inbred strain produced in Edinburgh, UK. Mapping rates to *Haemonchus placei* reference genome (BioProject PRJEB509) varied from 50.44 to 50.95%. These preliminary results show that the Brazilian *H. contortus* isolate is more related to the inbred strain and that there is a high genomic diversity in *H. contortus* species from different geographic regions. Furthermore, two different species (*H. contortus* and *H. placei*) from the same genus presented high genomic similarity.

15. Clinical validation of molecular markers of macrocyclic lactone resistance in *Dirofilaria immitis*

CRISTINA BALLESTEROS[1], **CASSAN N. PULASKI**[2], CATHERINE BOURGUINAT[1], KATHY KELLER[1], ROGER K. PRICHARD[1], TIMOTHY G. GEARY[1]

[1]INSTITUTE OF PARASITOLOGY, MCGILL UNIVERSITY, 21111 LAKESHORE ROAD, SAINTE ANNE DE BELLEVUE, H9X3V9, QC, CANADA [2]SCHOOL OF VETERINARY MEDICINE, LOUISIANA STATE UNIVERSITY, SKIP BERTMAN DRIVE, BATON ROUGE, LA 70803 USA

Prophylaxis with macrocyclic lactone (ML) endectocides is the primary strategy for heartworm control in companion animals, but recent evidence has confirmed that ML-resistant *Dirofilaria immitis* isolates have evolved in regions in the USA. Comparison of genomes of ML-resistant isolates demonstrates that they are genetically distinct from wild types. Previously, we identified single nucleotide polymorphisms (SNPs) which correlate with apparent ML resistance. Since reliable *in vitro* assays are not available to detect ML resistance in larvae or microfilarial stages, the failure to reduce microfilaraemia in infected dogs treated with an ML could be used as a clinical assay. The purpose of our study was to validate the genotype-phenotype correlation between SNPs associated with ML resistance and failure to reduce microfilaraemia following ML treatment, and to identify the minimal number of SNPs that could be used to confirm ML resistance. Kits were sent out to 29 participating veterinary clinics, each containing supplies for blood collection, ML dosing, and prepaid shipping. Dogs were recruited after diagnosis of patent heartworm infection, then treated with a standard dose of Advantage Multi® (label approved for the elimination of microfilariae) and a blood sample was taken pre- and 2-4 weeks post-treatment. Each sample was processed by performing a modified Knott's Test followed by microfilaria isolation, gDNA extraction, and MiSeq sequencing of regions encompassing 10 SNP sites, previously suspected as highly correlated with ML resistance. Data analysis has shown a good correlation of SNP loci frequencies with the ML microfilaricidal response phenotype. Although all predictive SNP combination models performed quite well, the 2-SNP model performed superior to other models tested and would be desirable to use further on a larger geographical scale in the future. Additional applications of the 2 most reliable SNPs is also underway and results will be presented if available.

16. Host defense versus immunosuppression: Unisexual infection with male or female *Schistosoma mansoni* differentially impacts the immune response against invading cercariae

MARTINA SOMBETZKI[1], NICOLE KOSLOWSKI[1], **ANNE RABES**[1], SONJA SENEBERG[1], FRANZISKA WINKELMANN[1], CARLOS FRITZSCHE[1], MICHA LOEBERMANN[1], EMIL C. REISINGER[1]

[1] DEPARTMENT OF TROPICAL MEDICINE AND INFECTIOUS DISEASES, UNIVERSITY MEDICAL CENTER ROSTOCK, GERMANY

Infection with the intravascular dioecious trematode Schistosoma spp. remains a serious tropical disease and public health problem in the developing world, affecting over 258 million people worldwide. During chronic *Schistosoma mansoni* infection, complex immune responses to tissue-entrapped parasite eggs provoke granulomatous inflammation which leads to serious damage of the liver and intestine. The suppression of protective host immune mechanisms by helminths promotes parasite survival and benefits the host by reducing tissue damage. However, immune suppressive cytokines may reduce vaccine-induced immune responses. By combining a single sex infection system with a murine air pouch model we were able to demonstrate that male and female schistosomes play opposing roles in modulating the host's immune response. Female schistosomes suppress early innate immune responses to invading cercariae in the skin and upregulate anergy-associated genes. In contrast, male schistosomes trigger strong innate immune reactions which lead to a reduction in worm and egg burden in the liver. Our data suggest that the female worm is a neglected player in the dampening of the host's immune defense system and is therefore a promising target for new immune modulatory therapies.

17. PD-L1-expressing group 2 innate lymphoid cells checkpoint Th2 cells during helminth infection

CHRISTIAN SCHWARTZ[1,*], ADNAN R. KHAN[1], ACHILLEAS FLOUDAS[1], SEAN P. SAUNDERS[1], EMILY HAMS[1], HANS-REIMER RODEWALD[2], ANDREW N.J. MCKENZIE[3], PADRAIC G. FALLON[1]

*SCHOOL OF MEDICINE, TRINITY BIOMEDICAL SCIENCES INSTITUTE, TRINITY COLLEGE DUBLIN ; [2]DIVISION OF CELLULAR IMMUNOLOGY, DKFZ, HEIDELBERG; [3]MEDICAL RESEARCH COUNCIL, LMB, CAMBRIDGE; *PRESENT ADDRESS: IFIZ, DEPARTMENT OF IMMUNOLOGY, EBERHARD-KARLS-UNIVERSITY TUEBINGEN*

Innate lymphoid cells are important contributors to type 2 immune responses associated with parasitic infections, allergies and asthma. Previous studies have shown that group 2 innate lymphoid cells license dendritic cells, express MHC class II molecules and promote Th2 polarization during infections with *Nippostrongylus brasiliensis* or protease allergen challenge. However, it remains unclear, which other factors contribute to the dialogue between ILC2 and CD4 T cells, and whether the crosstalk between T cells and ILC2s contributes to the full activation of effector T cells. We have identified the co-stimulatory molecule PD-L1 as an important factor promoting the full activation of IL-13-producing Th2 cells during infection with the gastrointestinal helminth *N. brasiliensis*. IL-33-activated ILC2 upregulate PD-L1 in an ST2-dependent manner. PD-L1-expressing ILC2 then promote the upregulation of the Th2 master transcription factor GATA3 and IL-13-production in $CD4^+$ T cells via PD-1-signaling. The PD-L1:PD-1-mediated interaction between ILC2 and T cells then leads to increased goblet cell hyperplasia and accelerated worm expulsion.

18. Single-sex infection with female *Schistosoma mansoni* cercariae mitigates hepatic fibrosis after secondary infection

NICOLE KOSLOWSKI[1], **MARTINA SOMBETZKI**[1], MICHA LOEBERMANN[1], ROBBY ENGELMANN[2], NIELS GRABOW[3], CHRISTOPH H.ÖSTERREICHER[4], MICHAEL TRAUNER[5], BRIGITTE MUELLER-HILKE[2], EMIL C. REISINGER[1]

[1]DEPT OF TROPICAL MEDICINE & INFECTIOUS DISEASES, [2]INSTITUTE OF IMMUNOLOGY,AND [3]INSTITUTE FOR BIOMEDICAL ENGINEERING, UNIVERSITY MEDICAL CENTER, ROSTOCK, GERMANY [4] INSTITUTE OF PHARMACOLOGY , MEDICAL UNIVERSITY, VIENNA, [5] HANS POPPER LABORATORY OF MOLECULAR HEPATOLOGY, DEPARTMENT OF INTERNAL MEDICINE III, MEDICAL UNIVERSITY, VIENNA, AUSTRIA

Schistosomiasis remains a major cause of morbidity and mortality, and in the tropics and subtropics in particular, infection rates are high. The efficacy of anthelmintic therapy is limited since it has no effect on immature parasite stages and does not prevent re-infection. The root cause of disease is a granulomatous hypersensitivity reaction to parasite eggs entrapped within the intestinal wall and small liver sinusoids. This reaction is mainly caused by CD4+ T cells of the subtype 2 and alternatively activated macrophages. As a repair response it suppresses inflammation but results in hepatic fibrosis (e.g. Symmer's pipe stem fibrosis), portal hypertension and its clinical sequelae, ascites and esophageal varices. The best long-term strategy to control schistosomiasis may be to develop an immunization. Therefore, we designed a two-step *Schistosoma mansoni* infection model to study the immune-stimulating effect of a primary infection with either male or female cercariae. We demonstrated that a primary infection with female *S.mansoni* cercariae leads to the suppression of TH2-mediated granuloma size, hepatic fibrosis and disease progression in bisexually challenged mice. This protection is associated with Retnla- and Ctla4-mediated TH2 suppression but not with a reduction in parasite load. Our findings provide evidence that protection against egg-induced granulomatous hyperreactivity is achievable by exploiting gender-specific differences between schistosomes.

19. Antigen specificity of the adaptive immune response against *Nippostrongylus brasiliensis*

NATALIE THUMA[1], DIRK MIELENZ[2] AND DAVID VOEHRINGER[1]

[1]DEPT OF INFECTION BIOLOGY, AND; [2]DEPARTMENT OF MOLECULAR IMMUNOLOGY, MEDICAL CLINIC III, UNIVERSITY HOSPITAL ERLANGEN AND FRIEDRICH-ALEXANDER UNIVERSITY ERLANGEN-NUREMBERG (FAU), 91054 ERLANGEN, GERMANY.

Gastrointestinal helminths are potent inducers of a type 2 immune response and are well known for their ability to modulate their host environment. The excretory/secretory products, that are released by helminths while migrating through their host, are key players in mediating this host-parasite interface. However, little is known about the helminth-derived antigens and it remains unclear which T and B cell epitopes are targeted by the adaptive immune response. We use the infection model of the rodent parasite *Nippostrongylus brasiliensis* to search for immunodominant antigens. In particular, we use polyclonal serum as well as newly generated monoclonal antibodies from *N. brasiliensis* infected mice, to investigate the antigen-specificity of these IgE and IgG1 antibodies. Western blot analysis of the mouse serum revealed a reactivity of mouse IgG1 as well as IgE against *N. brasiliensis* proteins, with a distinct and reoccurring band pattern. This indicates, that IgE and IgG1 antibodies are directed against the same or similar helminth-derived molecules. Further analysis will be performed to identify these antigens by mass spectrometry.

20. A comprehensive study of N-glycosylation of *Haemonchus contortus*

CHUNQUN WANG[1], WENJIE GAO[2], XIN LIU[2], MIN HU[1]

[1]HUZAHONG AGRICULTURAL UNIVERSITY, WUHAN, CHINA. [2]HUAZHONG UNIVERSITY OF SCIENCE AND TECHNOLOGY, WUHAN, CHINA

N-glycosylation is one of the most prominent post-translational modifications of proteins that plays pivotal roles in varieties of biological functions and processes. The studies in N-glycosylation of helminths have attracted attentions not just due to the characteristics of composition of N-glycosylation, but also because of their potential roles in new drug and vaccine development. *Haemonchus contortus* is an economically important blood-sucking nematode of ruminants with worldwide distribution. Previous evidences have indicated that several bioactive and immunogenic proteins in *H. contortus* are glycosylated. However, little is known about the nature of N-glycosylation of *H. contortus*, especially in this area of functional N-glycoproteomics. Here, we comprehensively mapped N-glycosylation of adult *H. contortus* using high-resolution mass spectrometry-based glycomics and proteomics, as well as lectin histochemistry to localize these glycoproteins on the *H. contortus* tissues. Results have shown that high mannose glycans are dominated in the N-glycan profiling that are expressed on intestine, gonad of *H. contortus* and lectin localization analysis confirmed the abundance of N-glycosylated proteins. We further enriched the glycoproteins using hydrophilic interaction chromatography with mass spectrometry and identified 559 N-glycosylated sites on 337 proteins expressed in *H. contortus*. Among these identified proteins, a large proportion of proteins are involved in metabolic processes. According to the functional enrichment analysis, 16 potential vaccine candidates with known immune modulatory properties were detected including aminopeptidases, zinc metallopeptidases, cysteine proteinases, galectin and pepsinogen. Meanwhile, we also revealed the glycosylation characteristics of many key molecules involved in the infective processes of this parasite. This study provides a comprehensive insight into the N-glycosylation composition of *H. contortus*, suggesting the importance of further explorations in examining glycosylation in the development of novel interventions against haemonchosis.

21. Recombinant *Fasciola gigantica* Ras-related protein Rab-10-like protein modulates various functions of goat peripheral blood mononuclear cells (PBMCs) in vitro

XING-QUAN ZHU[1], AI-LING TIAN[1], MINGMIN LU[2], XIAOWEI TIAN[2], SI-YANG HUANG[1], XIANGRUI LI[2], HANY M. ELSHEIKHA[3]

[1]STATE KEY LABORATORY OF VETERINARY ETIOLOGICAL BIOLOGY, LANZHOU VETERINARY RESEARCH INSTITUTE, CHINESE ACADEMY OF AGRICULTURAL SCIENCES, PR CHINA. [2]COLLEGE OF VETERINARY MEDICINE, NANJING AGRICULTURAL UNIVERSITY, PR CHINA. [3]FACULTY OF MEDICINE AND HEALTH SCIENCES, SCHOOL OF VETERINARY MEDICINE AND SCIENCE, UNIVERSITY OF NOTTINGHAM, UK.

Ras family protein is a key component of many signal transduction pathways and plays an important role in parasite growth and development. However, the functional effects of *Fasciola gigantica* Ras-related protein Rab-10-like (FgRab-10) on goat peripheral blood mononuclear cells (PBMCs) are unknown. The present study cloned and expressed *FgRab-10* gene, and explored the functional effects of recombinant FgRab-10 (rFgRab-10) protein after *in vitro* stimulation of goat PBMCs. The *FgRab-10* gene was 618 bp in length, encoding 205 amino acid residues with a molecular mass of ~23 kDa. Western-blot analysis using goat anti *F. gigantica* serum showed that rFgRab-10 protein had good immunogenicity. Its incorporation with goat PBMCs was observed by indirect immunofluorescence (IFA), and the result showed that rFgRab-10 protein can be combined with goat PBMCs. The rFgRab-10 protein significantly promoted the secretion of IL-2, IL-4, IL-10, TGF-β and IFN-γ in goat PBMCs, but significantly inhibited the proliferation of goat PBMCs. The rFgRab-10 protein also significantly promoted the migration of goat PBMCs. Total Nitric Oxide Assay Kit was used to detect the production of total Nitric oxide (NO) in goat PBMCs, and the result showed that rFgRab-10 protein could significantly promote NO production in goat PBMCs. Flow cytometry was used to examine the phagocytic ability of goat monocytes and apoptosis level of goat PBMCs, and the result showed that rFgRab-10 protein significantly promoted the phagocytic ability of goat monocytes and apoptosis level of goat PBMCs. Our study revealed that FgRab-10 protein is an important excretory-secretory protein of *F. gigantica* (FgESP) and can affect the immune response of the host. When it interacted with goat PBMCs, FgRab-10 showed significant immuno-promoting effects. This study laid the foundation for further elucidation of the mechanism of immune evasion, immune interference and immunosuppression after *F. gigantica* infection.

DELEGATE LIST

Nada	Abdel Aziz	Institute of Infectious Disease & Molecular Medicine, Cape Town. South Africa	nadabdelaziz@gmail.com
Jesuthas	Ajendra	University of Manchester, UK	jesuthas.ajendra@manchester.ac.uk
Tim	Anderson	Texas Biomedical Research Institute, San Antonio, USA	tanderso@txbiomed.org
Thomas	Baum	Iowa State University, USA	tbaum@iastate.edu
David	Bird	North Carolina State University, USA	bird@ncsu.edu
Jimmy	Borloo	Ghent University, Belgium	jimmy.borloo@ugent.be
Klaus	Brehm	University of Wuerzburg, Gemany	kbrehm@hygiene.uni-wuerzburg.de
Collette	Britton	University of Glasgow, UK	Collette.Britton@glasgow.ac.uk
Frank	Brombacher	University of Cape Town, South Africa	frank.brombacher@uct.ac.za
Nichola	Calvani	University of Sydney, Australia	nichola.calvani@sydney.edu.au
Julie	Claycomb	University of Toronto, Canada	Julie.Claycomb@toronto.ca
Celine	Cosseau	University of Perpignan, France	celine.cosseau@univ-perp.fr
Jim	Collins	University of Texas South Western Medical Center, USA	JamesJ.Collins@UTSouthwestern.edu
Dick	Davis	University of Colorado, USA	Richard.Davis@ucdenver.edu
Anja	de Lange	University of Cape Town, South Africa	anjadelange@gmail.com
Marta	de los Reyes	Technical University of Munich, Germany	marta.reyes.jimenez@tum.de
Samantha	Del Borrello	University of Toronto, Canada	sam.delborrello@mail.utoronto.ca
Benjamin	Dewals	Liege University, Belgium	bgdewals@uliege.be
Colette	Dissous	Institute Pasteur, Lille, France	colette.dissous@pasteur-lille.fr
Bonnie	Douglas	University of Pennsylvania, USA	bonniebd@pennmedicine.upenn.edu
Patrick	Driguez	Wellcome Sanger Institute, UK	pd7@sanger.ac.uk
Maria Adelaida	Duque Correa	Wellcome Sanger Institute, UK	md19@sanger.ac.uk
Jan	Dvorak	Czech University of Life Sciences Prague	hdvorak76@outlook.com

Alison	Elliott	MRC/Uganda Virus Research Institute	Alison.Elliott@mrcuganda.org
Santiago	Fontenla	Universidad de la Republica, Uruguay	sfontenla@fmed.edu.uy
Gisela	Franchini	Universidad de la Plata, Argentina	gfranchini@conicet.gov.ar
Alejandra Nahili	Giorello	Universidad de la Plata, Argentina	nahiligiorello@gmail.com
Niki	Gounaris	Imperial College London, UK	k.gounaris@imperial.ac.uk
Andrea	Graham	Princeton University, USA	algraham@princeton.edu
Christoph G.	Grevelding	Justus-Liebig-University, Giessen, Germany	christoph.grevelding@vetmed.uni-giessen.de
Simone	Haeberlein	Justus-Liebig-University, Giessen, Germany	simone.haeberlein@vetmed.uni-giessen.de
Eve	Hanks	University of Glasgow, UK	e.hanks.1@research.gla.ac.uk
William	Harnett	University of Strathclyde, UK	w.harnett@strath.ac.uk
DeBroski	Herbert	University of Pennsylvania, USA	debroski@vet.upenn.edu
Andrew	Hinck	University of Pittsbugh School of Medicine, USA	ahinck@pitt.edu
William	Horsnell	University of Cape Town, South Africa	wghorsnell@gmail.com
Kevin	Howe	EMBL European Bioinformatics Institute, UK	kevin.howe@wormbase.org
Min	Hu	Huazhong Agricultural University, China	mhu@mail.hzau.edu.cn
Brittany-Amber	Jacobs	The University of Cape Town, South Africa	jcbrri008@myuct.ac.za
Deirdre	Joy	National Institutes of Health, USA	djoy@mail.nih.gov
Brunette	Katsandegwaza	University of Cape Town, South Africa	ktsbru001@myuct.ac.za
Graham	Legros	Malaghan Institute for Medical Research, Wellington, New Zealand	glegros@malaghan.org.nz
Adrian	Leontovyč	Academy of Sciences, Czechia	adrian.leontovyc@centrum.cz
Roman	Leontovyč	Faculty of Science, Charles University, Prague, Czechia	leontovyc.roman@seznam.cz
Xiangyong	Liu	China Agricultural University	liuxianyong@cau.edu.cn
Phil	LoVerde	University of Texas Health Science Center, USA	loverde@uthscsa.edu

Sara	Lustigman	Lindsley F Kimball Research Institute, New York Blood Center, USA	slustigman@nybc.org
Tomáš	Macháček	Charles University, Faculty of Science, Prague, Czechia	tomas.machacek@natur.cuni.cz
Rick	Maizels	University of Glasgow UK	rick.maizels@glasgow.ac.uk
Kazuhiro	Nakano	EA Pharma, Japan	kazuhiro_nakano68@eapharma.co.jp
Simone	Niciura	Embrapa Pecuaria Sudeste, Brazil	simone.niciura@embrapa.br
Justin Komguep	Nono	University of Cape Town, South Africa	Justin.NonoKomguep@uct.ac.za
Mark	Pearson	James Cook University, Australia	mark.pearson@jcu.edu.au
Cassan	Pulaski	Louisiana State University, USA	cpulaski@vetmail.lsu.edu
Anne	Rabes	University Medical Center, Rostock, Germany	anne.rabes@uni-rostock.de
Faye	Rodgers	Wellcome Sanger Institute, UK	fr7@sanger.ac.uk
Marion	Rolot	Liege University, Belgium	mrolot@uliege.be
Stephanie	Ryan	James Cook University, Australia	stephanie.ryan2@my.jcu.edu.au
Irma	Schabussova	Medical University of Vienna, Austria	ischabuss@gmail.com
Christian	Schwartz	Trinity College Dublin, Ireland	christianschwartz23@gmail.com
Murray	Selkirk	Imperial College London, UK	m.selkirk@imperial.ac.uk
Paul M.	Selzer	Boehringer-Ingelheim Vetmedica GmbH, Germany	Paul.Selzer@boehringer-ingelheim.com
Catherine	Sharpe	University of Manchester, UK	catherine.sharpe@postgrad.manchester.ac.uk
Katherine	Smith	Cardiff University UK, and University of Cape Town, South Africa	smithk28@cardiff.ac.uk
Martina	Sombetzki	University Medical Center, Rostock, Germany	martina.sombetzki@uni-rostock.de
Adrian	Streit	Max Planck Institute for Developmental Biology, Germany	adrian.streit@tuebingen.mpg.de
Sutas	Suttiprapa	Faculty of Medicine, Khon Kaen University, Thailand	sutasu@kku.ac.th
Natalie	Thuma	University Hospital Erlangen Gemany	Natalie.Thuma@uk-erlangen.de

Patrick	van der Zande	Leiden University Medical Center, The Netherlands	h.j.p.van_der_zande@lumc.nl
Jérôme	Vicogne	Institute Pasteur, Lille, France	jerome.vicogne@ibl.cnrs.fr
Jianbin	Wang	University of Colorado, USA	jianbin.wang@ucdenver.edu
Si	Wang	China Agricultural University	wangsi923@sina.cn
Chunqun	Wang	Huazhong Agricultural University, China	wangchunqun@webmail.hzau.edu.cn
Mark	Wilson	Genentech, USA	wilson.mark@gene.com
Xing-Quan	Zhu	Lanzhou Veterinary Research Institute, Chinese Academy Of Agricultural Sciences	xingquanzhu1@hotmail.com