**1. A helminth malate dehydrogenase as novel regulator of type 2 immune responses**

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Helminth parasites are endowed with potent immunoregulatory effects enabling them to escape host immune responses and establish chronicity. We previously identified the cytoplasmic malate dehydrogenase (Eg-cMDH) and severin (Eg-SVN), from *Echinococcus granulosus sensu lato (E. granulosus s.l*), as biological biomarkers to predict early post-surgical outcomes of pediatric patients treated for cystic echinococcosis. Although displaying an important prognostic value, little is known about the immunoregulatory effects of these proteins, especially in type 2 immunity settings. Here, we produced Eg-cMDH and Eg-SVN recombinantly and investigated their immunoregulatory potential on human and murine macrophages. Our preliminary data indicate that Eg-cMDH modulates macrophage activation by up-regulating anti-inflammatory and type-2 suppressive mediators such as interleukin 10, IL-1β) and prostaglandin E2 (PGE2). In line, Eg-cMDH downregulates the expression of M2 markers including Mannose receptor C-type1 (MRC1). In contrast to Eg-cMDH, recombinant Eg-SVN, purified using the same protocol, showed no regulatory effects, on both human and murine macrophages. Thus, our preliminary results identify Eg-cMDH as a regulator of macrophage activation and suggest that multiple metabolic enzymes of helminth parasites can interfere with host type 2 immunity.

**2. Host-derived lipid mediators as novel regulators of Treg cell development with distinct features in maintaining immune tolerance during human helminth infection**

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Distinct tissue-derived signals drive regulatory T cell (Treg) induction and shape their heterogeneity and functionality in chronic inflammation. In the inflammatory parasitic brain disease, neurocysticercosis (NCC), we have recently identified that the lipid mediator $PGE_2$ secreted from parasitic-glutamate dehydrogenase (GDH)-modulated monocyte and microglia is a central driver of Treg development which is essential to control disease in asymptomatic, non-epileptic NCC patients. Here, we characterize the epigenetic and transcriptional determinants of GDH-$PGE_2$-modulated Treg cell development and the clinical implications in brain inflammation and silencing. Peripheral cells from healthy German and Tanzanian individuals and asymptomatic as well as anti-helminthic treated-symptomatic NCC patients were pulsed with recombinantly expressed parasite GDH or $PGE_2$, followed by in-depth immunophenotyping via FACS. Underlying mechanisms of lipid mediator modulation were further explored by transcriptional profiling of *ex vivo* sorted CD4 and monocytes alongside targeted LC/MS/MS profiling of serum eicosanoids, $PGE_2$-precursors and other metabolites. The epigenetic and transcriptional signatures of the *in vitro* induced Tregs were furthermore assessed via ATACSeq and RNASeq and compared to *ex vivo* sorted Tregs and Tconv from NCC patients and healthy individuals. *Ex vivo* Tregs of asymptomatic NCC patients and *in vitro* PGE2-induced Tregs share distinct features of enhanced central nervous system migration and endothelial cell adhesion ($CD69^{hi}$, $CCR7^{+}$, VLA-$4^{hi}$, LFA-$1^{+}$) alongside pronounced expression of Helios, ST2 and IL-35 as compared to very distinct IL-2-induced Tregs. This correlated with EP2 and EP4 receptor expression on naïve T cells and elevated $PGE_2$ and precursor metabolites in patients' sera, which declined following anti-helminthic treatment. Integrative sequencing analyses revealed the non-canonical TNFR2-NF-kB and JAK-STAT pathways as important regulators controlling PGE2-driven Treg differentiation alongside corresponding epigenetic landscape alterations. This work provides important insights into lipid mediators as novel regulators of Treg development with distinct features to maintain immune tolerance in NCC and possibly other inflammatory diseases.

### *3) Necator americanus* recombinant proteins as novel therapeutics for inflammatory disease

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Experimental and naturally acquired human helminth infections have been shown to impart varying degrees of protection against a suite of inflammatory diseases. The proclivity of helminths to regulate their host immune response and suppress inflammation is attributed to the active release of excretory/secretory proteins (ESP) into the host tissues. Experimental infection of humans with helminths presents significant complications as a therapeutic modality due to their complex lifecycles, likely poor adoption, and unavoidable side effects in some subjects. As such, there is now considerable interest in identifying bioactive ESPs and making them more drug-like. We therefore created a recombinant library of *N. americanus* ESPs from both the adult and larval stage secretomes and are screening the library in a range of *in vitro* and *in vivo* assays to identify proteins with potent immunoregulatory properties. Thus far, we have identified proteins that could form the basis of novel therapeutics for treating type 2 diabetes, inflammatory bowel disease and rheumatoid arthritis based on their *in vitro* and/or *in vivo* bioactivities.

## *4)* IPS-based pathophysiologically-relevant human liver co-culture microfluidic model for the study of its interactions with parasitic *Schistosoma mansoni* eggs

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To study *Schistosoma mansoni* development and reproduction with a new physiological paradigm, we have developed a microfluidic culture system able to host adult parasites. In our first instance, we used such devices to test antischistosomal drugs with improved sensibility. As the severity of schistosomiasis comes from the accumulation of eggs encysted in host tissues, mainly the liver, where a granulomatous immunological response is triggered, the interactions between the eggs and the hepatic tissue is central in the study of the disease, but it still lacks relevant *in vitro* models. Therefore, to mimic the liver microenvironment, we engineered a liver-on-chip device composed of hepatocytes, hepatic stellate cells and liver sinusoidal endothelial cells, in a hierarchical three-dimensional structure, reproducing the liver sinusoid architecture. The different cellular types are obtained by differentiating human induced pluripotent stem-cells, in order to obtain a relevant and immunologically coherent tissue. The structure of this microsystem is made of two nested polydimethylsiloxane parts. This perfused device is openable during experiments to easily implement the biological model and add the parasitic material. Importantly, the device provides *in vitro* dynamical conditions closer to the *in vivo* host microenvironment and should recapitulate the natural egg-liver interactions. Responses of the liver-on-chip to eggs presence is now explored to analyse the rise of the pathology in controlled environmental conditions, including hypoxia. In particular, the induced fibrotic process is evaluated by immunostaining and by monitoring secretions. Also, the embryonic development of eggs in contact with this assembled tissue is studied by staining with 5-ethynyl-2'-deoxyuridine (EdU) and assessing soluble egg antigens. This device could enhance the egg maturation process and lead to improved production of *in vitro* viable and infectious miracidiae. This controlled *in vitro* maturation of eggs could then be applied to generate CRISPR-Cas9 modified parasite strains, a major challenge in the field.

*5)* **Host specificity of the human parasite *Trichuris trichiura* is determined by the host microbiome**

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Human whipworms (*Trichuris trichiura*) are soil transmitted helminths that infect hundreds of millions of people worldwide and can cause Trichiuriasis, a major neglected tropical disease. Infection occurs through the ingestion of whipworm eggs, which subsequently hatch in the caecum and proximal colon, releasing larvae that establish themselves within the intestinal epithelium. Animal models of *Trichuris muris* (murine) and *Trichuris suis* (porcine) infection have been instrumental in elucidating the essential role of the host intestinal microbiota in whipworm egg hatching nonetheless, efforts to construct an infection model for studying *T. trichiura* have not yielded success. This has historically impeded investigations into host-microbiota-parasite interactions of the human whipworm infection. In this study, we aimed to investigate the key determinants of *T. trichiura* host specificity through the establishment of a laboratory model for human whipworm infection. Leveraging a humanised microbiota mouse model, we conducted *in vivo* infections with *T. trichiura* and performed *in vitro* egg hatching experiments using caecal samples. Remarkably, we achieved the first successful infection of a non-primate host with *T. trichiura* using this model. A comparative analysis of the bacterial composition in caecal samples from mice harbouring murine *versus* humanized microbiome led to the indentification of bacterial species implicated in *T. trichiura* egg hatching. Moreover, we observed *T. trichiura* first-stage larvae (L1) infection of murine caecaloids grown in transwells. Together, these results suggest that *T. trichiura* host specificity is determined by the host microbiome and not the host intestinal epithelium. To closely recapitulate host-*T. trichiura*-microbiota interactions, we are currently performing infections in human caecaloids. Collectively, these studies will result in the establishment of the first experimentally tractable system for the human whipworm infection, enabling the identification of key interacting molecules at the host-parasite-microbiota interface to be targeted for drug discovery, then the testing of novel therapies to tackle Trichuriasis.

**6) From genome to function, from invasion to evasion – deciphering the roles of Venom allergen-like proteins in *Schistosoma mansoni***

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Proteins from Venom allergen-like protein family are defined by a unique SCP/TAPS protein domain with a highly conserved α-β-α sandwich conformation. Because of this strong conservation of the tertiary structure and ubiquitous presence of these proteins in secretomes of helminths, it was suggested that all SCP/TAPS domain-containing proteins share a common but not elucidated biological activity possibly directly linked to a parasitic lifestyle. To date, 29 protein-coding SmVAL genes were identified in the *Schistosoma mansoni* genome, but over the years, so far only 4 of these proteins have been associated with any functional data. However, the quality of the parasite genome has significantly improved over the last decade and with the most recent version we were able to identify 35 SmVAL genes. Through consequent meta-analysis of freely available RNASeq data of ten *S. mansoni* life stages, we uncovered expression profiles of these genes across the life cycle with SmVALs being the most highly expressed in the parasite's eggs. With robust RNASeq differential expression analysis of eggs from liver and intestine we found out that SmVALs have distinct expression patterns depending on developmental stage of the egg, but also on the surrounding tissues. By adopting a multifaceted approach including protein expression of candidate egg and cercarial SmVALs in HEK293 cells, immunolocalization studies, immunological assays, protein-protein interactions and cell culture experiments we offer a robust insight into the role of these proteins in different stages of a parasite. While "egg" SmVALs seems to be employed by the miracidium larvae in the penetration of the intermediate host, cercarial VAL10 specifically alters local and global definitive host immune response, initiate ECM remodelling and stimulates angiogenesis. Our work provides crucial insights in the biological functions of these enigmatic proteins in different stages and provides a solid basis for further research endeavours.

## *7)* *Caenorhabditis elegans* as a Non-model Nematode - at least in glycomic terms!

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*Caenorhabditis elegans* is the genetically best-studied nematode; however, its N-glycomic complexity is actually baffling and after twenty years we have only now come close to showing the sheer variety of structures. Some features of its N-glycans are, to date, unique and include bisecting galactose and up to five fucose residues associated with the asparagine-linked $Man_{2-3}GlcNAc_2$ core; the substitutions include galactosylation of fucose, fucosylation of galactose and methylation of mannose or fucose residues as well as phosphorylcholine and fucose on antennal (non-reducing) *N*-acetylglucosamine. Only some of these modifications are shared with various other nematodes, while others have yet to be detected in any other species. Thus, *C. elegans* can be used as a model for some aspects of N-glycan function, but its glycome is far from identical to those of other organisms and is actually far from simple. Possibly the challenges of its native environment, which differ from those of parasitic or necromenic species, led to an anatomically simple worm possessing a complex glycome.

***8)*** **Putting meaningful antibody responses to *Schistosoma* glycan antigens in the spotlight**

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Schistosome infection induces a plethora of antibodies recognising a wide range of parasite antigens, including a large proportion of anti-carbohydrate (glycan) antibodies. The role of these anti-glycan antibodies in immunity remains poorly understood. Some are likely contribute to protective immunity or immunomodulatory effects, others may be irrelevant or give rise to an immunological smokescreen. Moreover, some glycan antigens are specific for schistosomes, but others are expressed also in subsets of other helminth species, microbes, plants, and (in)vertebrates including schistosome hosts. This raises additional questions regarding cross-reactivity of anti-glycan antibodies, both in the context of protective immunity and of their diagnostic potential. To address some of these questions we have carried out extensive glycomic analysis of *S. mansoni* and *S. haematobium* across the life cycle of the parasite, in combination with the application of glycan antigen microarrays to study antibody profiles in human and animal plasma samples. Taking advantage of longitudinal sample sets from single and repeated controlled human *S. mansoni* infections and from experimentally infected or immunised animals, as well as samples from schistosome endemic areas, we have determined total IgG and subclasses to a wide range of glycans. Responses were analysed for associations with markers of tolerance, protection and infection. Particularly, a wide range of fucosylated glycans antigens in schistosomes elicit high antibody titres in humans after single of multiple exposures, as well as in partially protected animals. These antigens are highly expressed on the larval stage of the parasite, which in an *in vitro* model is sensitive to damaging effects of fucose-specific antibodies. Other unique schistosome glycan antigens, such as CAA, give rise to a highly specific antibody response in recent but not chronic infections, providing a novel target for diagnostic serology. Current work and future plans on advancing these antigens as therapeutic or diagnostic targets is discussed.

***9)*How does a helminth parasite antagonize IL-33:ST2 signalling? A structural perspective**

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Helminth parasites modulate the host's immune response to allow their survival in the host. These modulation activities include the HpARI and HpBARI protein families from the murine intestinal nematode *Heligmosomoides polygyrus,* which bind and block IL-33 or its receptor (ST2), respectively. The binding of cytokine IL-33 to its cognate receptor ST2 triggers immune signalling that activates both type 2 immunity to parasitic helminths and allergic pathology. Here, we present the first detailed molecular characterisation of both the HpARI:IL-33 and the HpBARI:ST2 complexes, solved by X-ray crystallography and cryo-EM studies, respectively. Our structural characterisation has revealed the mode of action of HpARI, which forms a binary complex of a HpARI monomer interacting with the IL-33 monomer. HpARI binds to IL-33 through its CCP2 domain and prevents IL-33:ST2 interaction through a large loop in its CCP3 domain, which blocks the IL-33:ST2 interaction site. HpBARI, by contrast, is produced as a trimer which binds to three ST2 receptors in a planar formation. We propose that this hexameric complex structure allows for preferential targeting of membrane-bound ST2 rather than the soluble decoy form of ST2. Our structure-derived mutagenesis, biochemical, and immunological analysis provide a comprehensive understanding of the distinct mechanisms these two effectors use to disrupt host IL33:ST2 signalling, boosting helminth survival.

***10)*** **The *H. polygyrus* TGF-β mimic TGM1 exerts broad anti-inflammatory effects on multiple immune cell types**

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Helminth parasites dampen host immunity through the secretion of immunomodulatory proteins such as the family of TGF-β mimics (TGMs) of *Heligmosomoides polygyrus.* The prototypic member, TGM1, induces *in vitro* differentiation of murine and human Foxp3+ T regulatory cells through TGF-β receptor (TβR)/SMAD signaling, despite bearing no sequence similarity to host TGF-β. When transferred to mice, TGM1-induced Tregs can suppress autoimmune inflammation, and both oral and parenteral administration of TGM1 protein attenuates DSS and T cell transfer induced colitis in mouse models. In addition, TGM1 suppresses airway eosinophilia in mice sensitized to ovalbumin, house dust mite or the fungal allergen Alternaria. We noted that in the lattermost model, TGM1 suppressed eosinophilia within 24 hours of sensitization, indicating effects on either or both innate immune and epithelial barrier cells. Among innate cells modulated by TGM1, macrophages showed suppression of inflammatory cytokine production with enhanced Arginase-1 and IL-10 release, together with muted expression of surface markers required for antigen presentation to T cells. Modulation of epithelial cells was also establish in an organoid culture system of intestinal epithelial cells, in which *H. polygyrus* secreted products inhibit the differentiation of cell types most injurious to parasites, goblet cells and tuft cells. As TGF-β superfamily members are intimately involved in intestinal cell differentiation, we are now exploring the role of TGM family members in the epithelial stem cell response to infection.

**11) Modular *H. polygyrus* TGF-β mimic proteins molecularly mimic mammalian TGF-β, enabling effective immune-modulation, while limiting fibrogenesis**

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Helminths, which have co-evolved with their mammalian hosts over long evolutionary timescales, persist by secreting soluble factors that suppress key immune signaling pathways and modulate host immunity. In recent studies, we showed that the murine intestinal helminth *Heligmosomoides polygyrus* secretes a protein known as TGF-β mimic 1 (TGM1) that binds directly to the host receptors to activate the TGF-β pathway and suppress immunity. However, TGM1 is part of a larger family of proteins secreted by the parasite and recently we found that TGM6, which is co-expressed in adult worms with TGM1 and lacks domains 1–2 (D12) that binds TβRI, functions as a potent TGF-β inhibitor in fibroblasts, but not splenic T-cells. To gain insight into the molecular basis by which the TGMs engage host receptors, we mapped the binding sites on TβRI and TβRII using NMR and determined the structure of TGM6 D3 bound to TβRII using X-ray crystallography. This showed that the TGMs mimic the mammalian cytokine structurally by binding and engaging the same set of residues as TGF-β, but by using a complement control protein-like scaffold that has no structural homology to the TGF-β cystine-knot growth factor fold. To resolve the paradox of why the parasite might simulataneously produce and secrete TGF-β agonists and antagonists, we investigated the role of D45 and found that in agonists these mediate binding to co-receptors such as CD44, that are abundant on T-cells but absent on fibroblasts, while antagonists bind alternative co-receptors that are present on fibroblasts but absent on immune cells. The co-receptor mediated cell targeting, together with moderation of TβRII binding affinity, which further promotes differential targeting, may be part of a larger strategy the parasite uses to impart immunomodulatory TGF-β signalling without triggering fibrogenesis, the major adverse effect of any therapy with the mammalian cytokine.