The Global Challenges Research Fund

Strengthening capacity at the start of research careers: young researchers exchange program in parasitology.

What it is? This is a repeat of a very successful programme run last year by the University of Glasgow and the Wellcome Centre for Integrative Parasitology aimed at the young parasitology researchers from low- and middle-income African countries. It offers to a group of research students the opportunity to join one of the UoG parasitology teams for 3 months and work on a small individual research project. The students will acquire valuable experience in the international environment and will network and collaborate with both the researchers from the UoG and with each other.

What is covered? The scheme covers student's travel, accommodation and sustenance in Glasgow as well as part of the research costs (the remainder is covered by the team hosting the student)

Who is eligible? In order to apply for the scheme the student needs to:

- Be a citizen of an African low- or middle-income country
- Have at least a BSc degree in a relevant field (e.g. biology, biochemistry, medicine, veterinary medicine, public health or epidemiology) or equivalent research experience.
- Have a demonstrable interest and in parasitology or related field
- Be at the early stage of his/her research training (preferably not yet in the possession of a PhD)
- Be able to come to the UK for the period of January to March 2020 (includes being eligible for UK visitors visa)
- Secure a mentor in a recognised research unit based in African LMIC willing to recommend the student and provide intellectual support through the exchange.

How to apply? The student needs to:

- Choose a research project from the provided list (alternatively students are welcome to contact one of the participating parasitologists from the University of Glasgow proposing their own project)
- Fill the application form (including the section filled by the student mentor)
- E-mail the filled application and short CV to the following address gcrf.exchange.glasgow@gmail.com.

The deadline for application is **05.11.2019.** Any questions regarding the scheme should be directed to **katarzyna.modrzynska@glasgow.ac.uk**. Questions regarding individual research projects should be directed to potential supervisors.

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Project 1	
Investigating the molecular mechanism of human infectivity of *Trypanosoma brucei gambiense* , the causative agent of African sleeping sickness	
Supervisor Name	**Contact E-mail**
Annette MacLeod	Annette.macleod@glasgow.ac.uk

Description:

Trypanosoma brucei is the causative agent of African sleeping sickness in humans and one of several pathogens that cause the related veterinary disease Nagana. A complex co-evolution has occurred between these parasites and humans that led to the emergence of trypanosome-specific defences and counter-measures. The first line of defence in humans is the trypanolytic protein apolipoprotein-L1 (APOL1) found within two serum protein complexes, trypanosome lytic factor 1 and 2 (TLF-1 and TLF-2). Two sub-species of *T. brucei* have evolved specific mechanisms to overcome this innate resistance, *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*. In *T. b. rhodesiense*, the presence of the serum resistance associated (SRA) gene is sufficient to confer resistance to lysis. The resistance mechanism of *T. b. gambiense* is more complex, involving multiple components: reduction in binding affinity of a receptor for TLF, increased cysteine protease activity and the expression of *T. b. gambiense*-specific glycoprotein (TgsGP).

Recently, our collaborator has discovered yet another mechanism of resistance to the lytic effects of human serum in the most clinically relevant sub-species, *Trypanosoma brucei gambiense*. This mechanism involves the expression of a mannose binding lectin by the parasite.

In this project the student will make recombinant protein of wild-type and variant forms of the mannose-binding lectin in a eukaryotic expression system, LEXY, and test these variants for their ability to bind their protein partner and prevent lysis.

The student will design variants proteins through an analysis of key residues in the protein structure, learn good laboratory practice in tissue culture, perform protein purification, design and conduct lysis inhibition assays using the recombinant proteins. In addition to laboratory skills, the student will also learn transferable skills such as effective communication & presentation skills and report writing.

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Project 2	
The role of ATR kinase activity in VSG switching in *Trypanosoma brucei*	
Supervisor Name	**Contact E-mail**
Richard McCulloch & Tansy Hammarton	Richard.McCulloch@glasgow.ac.uk Tansy.Hammarton@glasgow.ac.uk

Description:

All pathogens must survive immunity to prosper within and spread between their hosts. Antigenic variation (AV), involving surface antigen switching to evade adaptive immunity, is a particularly widespread survival reaction, found in viral, bacterial and eukaryotic pathogens.
In *T. brucei,* AV of its variant surface glycoprotein (VSG) coat has evolved remarkable mechanistic complexity, relying on a repertoire of >2000 *VSG* genes and 'pseudogenes' [1]. Only a single VSG is expressed at a time on any given cell, since the sole transcribed *VSG* must reside in a '*VSG* expression site (ES)', which is a telomeric, multigene, RNA Polymerase I-transcribed genome feature. However, *T. brucei* contains not just one *VSG* ES, but many [2]. As a result, *T. brucei* may execute a switch in VSG coat composition in two ways: by silencing the actively transcribed ES and activating transcription from one other ES, or by recombination of a silent *VSG* into the active ES. These reactions appear mechanistically distinct, but such a view must be tempered by a lack of understanding of how they are initiated and regulated. Despite extensive data on the catalysis of AV in eukaryotic pathogens, little is known, in any organism, about the signalling reactions that recognise the event(s) triggering surface antigen gene expression switching, or that integrate the reaction into their cell and life cycles.

The ATR kinase is a known component of the eukaryotic DNA damage repair machinery, and might be predicted to play a role in VSG switching. Intriguingly, data from the McCulloch lab has shown that RNAi-mediated depletion of *T. brucei* ATR not only increases DNA recombination but also leads to impaired *VSG* transcriptional control, disrupting *VSG* monoallelic expression, suggesting TbATR is a key part of the AV signalling machinery [3]. In this project, the effects of inhibiting TbATR activity will be investigated. Available anti-mammalian ATR inhibitors, some of which are being trialled for cancer therapies, will be tested in *T. brucei*, assessing their effect on cell viability (growth curves/determining EC50 values by Alamar blue assay). Further, their activity against TbATR will be determined by performing kinase assays on immunoprecipitated ATR and analysing changes to EC50 values upon depletion or overexpression of ATR. The phenotypic similarity of ATR inhibition to ATR depletion will be investigated by analysing cell cycle progression, levels of DNA damage marker, γH2A (immunofluorescence and western blot) and genome localisation of γH2A (ChIP). Finally, we will ask if the compounds impede AV using RT-qPCR of ES VSGs, RNAseq, and immunofluorescence of the VSG coat.

1. McCulloch R et al. *Microbiol Spectr* 2015, 3:MDNA3-0016-2014.
2. Hertz-Fowler C et al. *PLoS ONE* 2008, 3:e3527.
3. Black J et al. bioRxiv 2018, 435198; doi: https://doi.org/10.1101/435198

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Project 3	
Ookinete development in the malaria parasite: is culture flask as good as the mosquito?	
Supervisor Name	**Contact E-mail**
Katarzyna Modrzynska	katarzyna.modrzynska@glasgow.ac.uk

Description:

A key part of the malaria parasite's complex life cycle, is the transition from the mammalian host to a mosquito vector. After the blood meal, the specialised transmission stages of *Plasmodium* (gametocytes) emerge from the infected red blood cells in the mosquito midgut, fertilise, and transform into elongated motile forms called ookinetes. These can further develop ultimately leading to the next infection. The ookinete formation process is the main bottleneck of *Plasmodium* life cycle and potentially a perfect target for badly needed transmission-blocking interventions. At the moment, however, it remains largely understudied.

As the extraction of the ookinetes from mosquitoes is laborious and technically challenging, usually an *in vitro* culture of the rodent malaria model *P.berghei*, is used to generate a large number of these stages for laboratory studies. It is not known, however, how well the dynamics of the ookinete development in this setting mimics the one which takes place inside of an insect, as some genes showed significantly different expression profiles during the *in vitro* and *in vivo* development.

In order to address this issue the student will generate the samples for transcriptome analysis from different time points of the ookinete development. The samples will be either purified form the ookinete culture (*in vitro* time-course) or extracted from the mosquitoes midguts (*in vivo* time-course). They will be used generate the RNA-seq libraries, which will be sequenced and analysed comparing the ookinete development in both conditions. The experiment will identify the genes and processes differentiating the two environments, and chart the time-course of the ookinete development in both settings.

The student selected for the project will receive training in the maintenance of *Plasmodium* life cycle in laboratory conditions, mosquito dissections, various methods of RNA isolation and RNA-seq library preparation. RNA-seq data analysis training will also be provided to a student with some pre-existing knowledge of basic bioinformatics tools.

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Project 4	
Dissecting the functional structure of a parasite cytokine mimic	
Supervisor Name	**Contact E-mail**
Rick Maizels	rick.maizels@glasgow.ac.uk

Description:

Successful parasites must negotiate, and manipulate, the host immune system. In the case of helminth parasites, the host's own suppressive mechanisms are activated, through the induction of Regulatory T cells (Tregs). We have established that Treg induction in the model system intestinal parasite Heligmosomoides polygyrus is mediated by a family of parasite-encoded mimics of transforming growth factor-beta (TGF-beta); these products, named TGM, engage the host TGF-beta receptor to drive Treg differentiation. The project aims to study the key domains and amino acid residues of TGM family members by expressing recombinant proteins lacking one or more domains of the full length 5-domain protein, or by mutating key residues that are predicted from structural information to be essential for receptor binding. Functional properties of mutated proteins will be measured by activation of a reporter cell line, as well as ability of the proteins to drive Treg differentiation in vitro.

The student will acquire a range of skills in molecular and cellular parasitology, including designing a variety of gene constructs encoding the desired proteins, their expression in mammalian cells grown in sterile tissue culture, as well the use of reporter cell lines and primary T cell cultures assayed by flow cytometry.

Relevant references :

[1] Johnston, C.J.C., Smyth, D.J., Kodali, R.B., White, M.P.J., Harcus, Y., Filbey, K.J., Hewitson, J.P., Hinck, C.S., Ivens, A., Kemter, A.M., Kildemoes, A.O., Le Bihan, T., Soares, D.C., Anderton, S.M., Brenn, T., Wigmore, S.J., Woodcock, H., Chambers, R.C., Hinck, A.P., McSorley, H.J., and Maizels, R.M. (2017) A structurally distinct TGF-β mimic from an intestinal helminth parasite potently induces regulatory T cells. . Nature Communications 8 :1741

[2] Smyth, D.J., Harcus, Y., White, M.P.J., Gregory, W.F., Nahler, J., Stephens, I., Toke-Bjolgerud, E., Hewitson, J.P., Ivens, A., McSorley, H.J., and Maizels, R.M. (2018) TGF-beta mimic proteins form an extended gene family in the murine parasite Heligmosomoides polygyrus. Int J Parasitol 48 379-385

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Project 5	
Analysing scRNA-Seq in Host and Parasites	
Supervisor Name	**Contact E-mail**
Thomas Otto	Thomasdan.otto@glasgow.ac.uk

Description:

Background, summary of the project, techniques student will employ, anticipated outcomes, if appropriate any requirements regarding student's background and experience

Single cell RNA-seq represents an exciting new technology to understand the expression of single cells in host and parasites. Many different data sets are being generated, but they are just analysed with the bare minimum. In this project we will aim to re-analyse data, understand better the different subpopulations and find potential reasons how deep the populations should be clustered. Further we will use different methods to perform pseudo time analysis to detect marker genes for the different development stages.

The outcome of this analysis is to train the student in single cell analysis and to learn the latest technics. A potential scientific output would be to find new genes interacting between sub populations are that are crucial for the temporal development of parasite or immune system.

We would expect that the student to have a high affinity to work with R and parasite or immunological interest. Prior basic knowledge (like a R) would be of benefit.

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Project 6	
Exploring Nectroptosis as a mechanisms for clotting and blood brain barrier breakdown in cerebral malaria.	
Supervisor Name	**Contact E-mail**
Christopher Moxon	Christopher.moxon@glasgow.ac.uk

Description:

My group works on cerebral malaria – a devastating disease caused by Plasmodium falciparum. We are interested in finding out how the parasite causes clotting and leak in blood vessels in the brain. This project will focus on a potential mechanisms – through the parasite causing "necroptosis" in the endothelial cells that line brain blood vessels. We will do this using archived tissue from autopsies of children who died from cerebral malaria. The project will involve multiplex immunostaining in tissue and advanced imaging methods.

Necroptosis is a regulated form of cell death, morphologically characterized by cell and organelle swelling, which ultimately culminates in loss of plasma membrane integrity. Recent studies have linked endothelial cell necroptosis to breaks in vascular endothelium, activation of clotting cascade and organ damage. Additionally, deregulation of necroptosis has been linked to other cerebral conditions including neurodegenerative disorders and brain cancers as well as infectious diseases eg., meningitis or sepsis.

The aim of this project will be to: 1) define necroptosis status in tissues collected from cerebral malaria patients; 2) link necroptosis status to endothelial damage associated with malaria infection and to focal areas of parasite sequestration in tissue

Techniques: Immunofluorescence assays in paraffin fixed tissues will include RIP1K, RIPK3, MLKL, phospho-MLKL (Ser358, Thr357) to determine activation status and Caspase8 (inhibitor of necroptosis).

Targets of interest could be followed up at the transcription level using RNAscope technology.

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Project 7	
Ironing out the gaps in *Toxoplasma gondii:* determining the function of ZIPCO, a putative iron transporter	
Supervisor Name	**Contact E-mail**
Clare Harding	Clare.harding@glasgow.ac.uk
Description:	
Iron is an essential factor in all living cells, and yet is toxic in large quantities. Cells have evolved elaborate mechanisms for iron sensing, uptake and storage to avoid these problems. However, in the parasite *Toxoplasma gondii,* we don't yet know anything about how this intracellular parasite is able to steal iron from its host cell. This is important both because *T. gondii* is an important pathogen of both humans and animals, and is closely related to the parasite which causes malaria. By understanding how T. gondii utilises iron, we hope to find novel vulnerabilities which we can use to develop new strategies for malaria treatment. This project will focus on the characterisation of a possible iron transporter named ZIPCO which has never been studied in *T. gondii*. To understand the function of ZIPCO, we will use CRISPR/Cas9 to fluorescently tag the protein and find its localisation using wide-field, super-resolution and live cell microscopy. We will also create a conditional knockout of the gene and use multi-well plate assays to find its role in growth, both in normal conditions and when exposed to high or very low levels of iron. This project will include extensive cell culture of mammalian cells and *T. gondii*, molecular biology including cloning, genetic manipulation of *T. gondii* using CRISPR, microscopy, western blotting and dose-response assays.	

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Project 8	
Modulation of protein expression during Leishmania development	
Supervisor Name	**Contact E-mail**
Richard Burchmore	richard.burchmore@glasgow.ac.uk

Description:

Leishmania promastigotes develop from amastigotes to metacyclic forms that are infectious to the mammalian host. This development is evident from morphology and metabolism and must be underpinned by changes in protein expression. The proteomes of various Leishmania stages have been investigated by a variety of proteomic approaches but such comparisons have mostly been between life cycle extremes, such as promastigote and amastigote.
New multiplexable isobaric tagging approaches allow this data to be collected with higher temporal resolution. This offers the potential to reveal markers from different stages in promastigote development which, hitherto for, have been recognised primarily by rather subjective morphological assessment.
This project will involve establishment of an axenic culture of amastigotes. Amastigotes will be transferred to promastigote culture medium, triggering transformation to promastigotes. This culture will be sampled every 24 hours to generate material throughout promastigote development. Protein extracts will be labelled with 10 plex isobaric tags and proteins identified and quantified by mass spectrometry. The data obtained will be analysed with ProteomeDiscoverer software, and protein expression trends will be categorised, to protein markers that correlate with time points enriched for different promastigote stages.

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Project 9	
Investigating the interplay between malaria parasite infection and insecticide response in Anopheles mosquitoes	
Supervisor Name	**Contact E-mail**
Francesco Baldini	Francesco.Baldini@glasgow.ac.uk

Description:

Mosquitoes are responsible for the spread of diseases like dengue, yellow fever, ZIKA, and malaria. Malaria alone causes 429,000 deaths each year, mainly in children under 5. Current control methods for malaria focus on the use of insecticides (applied to bed nets and house walls). However, most mosquito vectors have now developed resistance against commonly used chemicals. If left unchecked, insecticide resistance (IR) could lead to a public health catastrophe with substantial increase in human mortality.

A novel possibility is to reduce the susceptibility of IR mosquitoes to infection; even if they survive insecticide exposure. Recent evidence suggests that the biological processes responsible for either susceptibilty to malaria, or to insecticides, are interlinked. Therefore, the ability of IR vector to become infected by malaria could be altered by sub-lethal insecticide exposure. However, the direction of these associations are not yet fully understood.

This project aims to understand the consequences of insecticide exposure on the ability of mosquitoes to transmitt malaria to predict the impact of IR on disease transmission and inform vector control programmes.

Specifically, multi-resistant *Anopheles gambiae* mosquitoes will be expose to insecticides and infected with the human malaria parasite *Plasmodium falciparum*; then 1) life history traits (fecundity and survival) and 2) parasite susceptibility (oocysts prevalence and intensity) will be quantified. The student will be trained on malaria parasite gametocyte culture and mosquito infections; mosquito rearing; measurement of mosquito malaria infection and life-history traits; statistical analysis; science communication.

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Project 10	
Epigenetics of the onset of malaria parasite transmission	
Supervisor Name	**Contact E-mail**
Andy Waters	Andy.Waters@glasgow.ac.uk

Description:

Background: Transmission of malaria is initiated in the blood stream at the point that the asexually growing and dividing *Plasmodium* parasite initiates an alternative developmental pathway to produce male and female gametocytes (a process called gametocytogenesis). Recent discoveries have pinpointed one critical event is the expression of a transcription factor called AP2-G which is responsible for initiating the transcription pattern that will leads to the development of both male and female gametocytes. Attention now switches to the control of the expression of AP2G itself. This is likely to be regulated in a number of ways:

1. A basal low rate of expression that peaks sufficiently in certain cells to allow commitment.
2. Epigenetic control of the expression level through the regulation of chromatin accessibility at the *ap2-g* locus (shown in human malaria parasite, *P. falciparum* [PF] although this is not yet established in the rodent malaria parasite, *P. berghei* [PB]).
3. Environmental control where proxies are sampled by the gametocyte triggering signaling pathways that impact upon epigenetics. One such proxy is lysophosphatidyl choline that acts upon PF but not PB.

P. knowlesi [PK] (the 5th human infectious malaria parasite) has recently been adapted for culture in human erythrocytes but currently does not make observable numbers of gametocytes.

Project: We wish to establish the role of epigenetic regulators on gametocytogenesis in PB (and PK). This project will focus on the role of acetylation and the enzymes responsible for the addition (transferases) and removal (deacetylases) of this modification that typically affects lysine residues in the histone tails of the nucleosome that is the basic building block of chromatin. Such proteins of interest are typically examined in a number of ways such as deletion of their encoding gene, tagging of the gene with GFP for visualisation purposes. The project will involve generation of DNA constructs in E.coli that can be introduced into either PB or PK to tag/ko two orthologous genes that are responsible for (Scott). The modified parasite lines will be verified for accuracy of modification and then examined for alterations to their phenotype such as the ability to produce gametocytes.

The candidate will gain experience in basic molecular biological procedures such as DNA cloning, PCR, microscopy and western blot analysis.

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Project 11	
Measuring anti-gametocyte immunity in controlled human malaria infections in Kenya	
Supervisor Name	**Contact E-mail**
Matthias Marti	Matthias.Marti@glasgow.ac.uk
Description:	
The study is aimed at measuring acquisition of transmission blocking (anti-gametocyte) immunity in a naturally exposed cohort in Kilifi Kenya with tight sampling. We have measured parasitemia and gametocytemia as well as gametocyte maturation rates by QRT-PCR. These measures will enable us to generate a model of gametocyte formation and maturation in a naturally exposed population. We will measure serum responses to asexual parasites and gametocytes by flow cytometry for samples that are PCR positive. Serum samples that are reactive to the surface of gametocytes will be screened for functional antibodies in complement fixation and phagocytosis assays. This study will enable examination of dynamics of anti-gametocyte responses and the effect of this responses on gametocyte maturation, a proxy for transmission.	

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Project 12	
Genetic and phenotypic analysis of growth rates in human malaria parasites	
Supervisor Name	**Contact E-mail**
Lisa Ranford-Cartwright	Lisa.ranford-cartwright@glasgow.ac.uk

Description:

Research in my laboratory links phenotypic differences in lines of human malaria parasites (*Plasmodium falciparum*) with variations in the parasite genes that control these traits. The parasite characteristics to be studied in this short project include different aspects of growth during intra-erythrocytic stages of the parasite, such as the number of merozoites produced within each schizont, the time for a complete cycle of development, and the invasion success of merozoites, and the multiplicity of invasion. Variation in each of these traits contributes to faster or slower growth in the body, which itself is associated with pathological differences in the infections.

The phenotypic characterisation will be carried out using *in vitro* cultures, using protocols we developed for this purpose. You will learn how to tightly synchronise parasites, and how to monitor their growth over several cycles of invasion. The phenotypic characterisation will be accompanied by analysis of candidate genes discovered in our previous research to control these traits, using molecular techniques including PCR amplification, cloning and sequence analysis, and analysis of gene expression levels by quantitative reverse-transcriptase PCR (qRT-PCR).

The parasites are recently isolated, and as yet unstudied, isolates and clones from asymptomatic individuals from malaria-endemic countries in Africa. We are investigating potential links between growth rates and the parasitaemia in the original donors, to try to understand the different outcomes of infection in human hosts.

Student background: students would benefit from some background in molecular skills and/or tissue culture, but full training can be given. Individuals who do not have a spleen are at greater risk when working with live malaria parasites, as are pregnant women, and so we advise against this project if you are in one of these categories.

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Project 13	
Does manipulation of Macrophage progenitor cells affect the macrophage's ability to respond to *Leishmania mexicana*?	
Supervisor Name	**Contact E-mail**
Megan MacLeod	Megan.macleod@glasgow.ac.uk
Description:	

Background: Parasites, such as *Leishmania mexicana,* have evolved over thousands of years to survive within host cells. To counter this, hosts have adapted to try to control the parasite. This ability to control infection is influenced by many factors, including the cell's activation status prior to infection. It is becoming clear that previous infections and the host's microbiome affect cells within tissues that parasites target, and also progenitor immune cells found in the bone marrow. It is hypothesised that low level 'tonic signals' delivered by microbial products or cytokines, enable immune cells and their progenitors to respond appropriately to subsequent pathogen challenge.

Aims: This project aims to use an *in vitro* model of macrophage differentiation to investigate the effects of low level tonic activation on progenitor cells. We hypothesis that prior treatment of progenitor cells with 'tonic signals' will alter the response of subsequently differentiated macrophages to parasite infection.

Method and learning outcomes: The student will learn *in vitro* tissue culture techniques required to maintain macrophage progenitor cells, how to differentiative these cells into macrophages, and how to propagate *L. mexicana*. We will then use flow cytometry and ELISAs to measure the responses of differentiated macrophages to *L. Mexicana* infection. This project will, therefore, provide training in a range of different immunology techniques, and teach the student how to analysis and present different types of data relevant to many immunology research projects.

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Project 14	
Interaction between infectious and autoimmune diseases	
Supervisor Name	**Contact E-mail**
Paul Garside	Paul.garside@glasgow.ac.uk
Description:	
The appears to be an increasing burden of non-communicable disease (NCD) in low and middle income countries (LMIC) as populations urbanise and lifestyles change. However, there remains a considerable infectious disease burden. However, the consequences of the interaction between non communicable and infectious diseases remains unclear. For example, it has been proposed that malaria infection may be immunosuppressive and reduce the prevalence of arthritis in endemic areas though this remains controversial. To examine these disease interactions in more detail this project will employ murine models of malaria infection and rheumatoid arthritis to examine effects on a variety of autoimmune parameters. This will then be linked to clinical cohort studies with collaborators in endemic countries. Techniques to be employed will include flow cytometry, ELISA, Luminex and immunohistochemistry. It is hoped that the project would provide preliminary data to support further studies. Some background in immunology and laboratory work would be useful.	

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Project 15	
Evidence for embryostasis vs rapid reinfection with schistosomes	
Supervisor Name	**Contact E-mail**
Poppy Lamberton	Poppy.Lamberton@glasgow.ac.uk
Description:	
In hyperendemic schistosomiasis regions, humans begin to shed eggs as soon as 21 days after praziquantel treatment. Whether these are eggs from juveniles that have developed (rapid reinfection) or from adults surviving treatment (resistance/embryostasis) is not yet known. Because adult schistosome worms are inaccessible in human hosts, we must use genetics of the offspring (eggs or miracidia) to infer adult genotypes. In this project, you will use microsatellites and other genetic markers with miracidia to characterise the adult populations pre- and post- treatment. You will have access to miracidia from a unique cohort of children sampled up to twice weekly from pre- to five months post-treatment. You will learn both genetic and bioinformatic analysis to understand dynamics of schistosome populations undergoing treatment.	