Name	JEAN LANGHORNE
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	1998

Career History

1973-1976: PhD student, MRC Clinical Research Centre, London
1976-1979: Research Assistant, Dept Chemical Pathology Guys, Hospital Medical
1979: PhD University College London
1979-1981: Member of staff, Basel institute for Immunology, Basel, Switzerland
1981-1984: Postdoctoral Fogarty Fellow, LMI, NIAID, NIH, USA
1984-1995: Group leader, Max Planck institute for Immunobiology, Freiburg, Germany
1995-1998: Lecturer/Reader in Immunobiology Imperial College, London

Major Awards, Honours and Prizes

EMBO-BioMalPar Lifetime Achievement Award (2016) for outstanding work in the field of malaria immunology
Wellcome Trust Senior Investigator Award (2015)

Membership of external committees, editorial boards, review panels, SABs etc

- Panel member (2020-) EU Evaluation Board “Immunity and Infection” for Advanced ERC Grants.
- Member Early Career Fellowship Selection Committee (2020-) Wellcome Trust/DBT India Alliance.
- Chair, Expert Review Group (2014-2017), Immune Systems in Health and Disease, Wellcome Trust, UK.
- Review Panel member (2016), International Research Training Group on Malaria, German Research Foundation (DFG) Germany.
- Panel member, Expert Review Group (2011-2014), Immune System in Health and Disease Wellcome Trust, UK.

Editorial boards
2000- present: Associate Editor, PLoS Pathogens
2019-present: Advisory Board , Trends in Immunology:
2019-present Editorial Board, Current Research in Immunology

Lab Name	***Malaria Immunology Laboratory***

Research programme and achievements

Interactions of the malaria parasite, *Plasmodium*, with its mammalian host has different outcomes depending on both parasite and host factors. My research seeks to understand the mechanisms of protective immunity to malaria, and the contribution of the host response to severe malaria disease. We use a mouse model of *Plasmodium chabaudi* (*Pc*), and link this as far as possible to studies of the immune response of humans exposed to *P. falciparum (Pf)* malaria.

The Plasmodium interspersed repeat (*pir*) gene family is the largest multigene family in *Plasmodium* species and has no known function. We have studied *pir* genes in the rodent parasite, *Pc*, as potential variant antigens and virulence factors. *Pir* expression is affected by transmission through the mosquito, and there was a strong association between *pir* expression and parasite virulence in the mouse. Increased *pir* transcription associated with avirulent infections, whereas chronic-stage parasites expressed fewer *pirs* and were more virulent. Unexpectedly, changes in *pir* expression in chronic infection were not selected by adaptive immunity suggesting that this multigene family may not be involved in classical antigenic variation and immune evasion, but may be involved in parasite virulence and immunopathology.

In our *Pc* model, IL-21 and T follicular helper (Tfh) cells are critical for controlling chronic infection. Furthermore, IL-21 has an additional role independently of Tfh/B cell interactions, in eliminating chronic infection. Using a *Pc*-specific Immunoglobulin knock-in mouse, we showed that atypical B cells, thought to be an indicator of an ineffective B-cell response resulting in chronic infection, are generated. Rather, they are short-lived plasmablasts that appear as a result of, not the cause of, chronic stimulation.

In human *Pf* malaria we set out to understand how frequent clinical *Pf* malaria episodes affect the immune system. We used whole blood transcriptomic-, cellular and plasma cytokine analyses on children living with endemic malaria under active surveillance for malaria for eight years. We found that multiple malaria episodes associate with modification of the immune system. Children who experienced a large number of episodes (>8) demonstrated upregulation of interferon-inducible genes, a clear increase in circulating levels of the immunoregulatory cytokine IL-10 and enhanced neutrophil, B- and CD8+ T cell activation. Such immune modifications may have implications for the initiation of protective immunity, and induction of vaccine-mediated protection.

In the future, we will study the relationship between *pir* genes and the host response, virulence and chronicity of infection and begin to elucidate the function(s) of the *pir* multigene family.

Transcriptional profiles of *pir* genes in different life-cycle stages will determine whether *pirs* are differentially transcribed in infection. Using specific antibodies and *in situ*-tagged *pir* genes, the subcellular location of PIR proteins at different life-cycle stages will be determined. If PIRs are located on the RBC surface, we will determine whether they interact with other host proteins (e.g. for sequestration). We have observed that the spleen is critical for development of immunity, and that parasites, particularly after mosquito transmission sequester there. We will investigate whether *pir* expression on/in infected RBC and virulence of the infection is affected by splenectomy, and whether *pirs* are responsible for splenic sequestration of infected RBC, and/or for stimulating innate immunity.

We will determine whether atypical B cells contribute to the protective B-cell response by production of affinity-matured protective antibodies in *Pc* infections. We will also examine the ability of human atypical B cells to produce functional *anti-Plasmodium* antibodies. Specificity of anti-*Plasmodium* antibodies in children acquiring immunity under different

epidemiological settings, will be carried out to determine whether specificity, amount, and/or breadth of the response are important for immunity.

Burkitt's lymphoma (eBL), a germinal-centre-derived B-cell lymphoma characterised by chromosomal translocation and activation of c-Myc, is strongly linked to *Pf* infection and Epstein Barr Virus (EBV). EBV is known to drive B-cell lymphomagenesis, but the interplay with *Pf* in eBL is unknown. With Dinis Calado, we will study eBL with a newly established mouse model of BL in which GC B-cell-specific *MYC* overexpression and constitutive PI3K-pathway activation is driven by immunisation. This generates lymphomas with similar morphology and mutations to human eBL. These tumour-prone mice will be infected with *Pc* +/- MHV68 (a γherpes virus related to EBV), to address the impact of *Plasmodium* infection on GC B-cell processes, tumour-latency, severity and genetic make-up, compared to non-malaria driven lymphomas. We will examine the *Pc*-specific B-cell response during infection, by crossing the *Pc*-specific immunoglobulin knock-in mouse with the BL mouse to generate a model that enables tracking of *Pc*-specific B cells before and after lymphoma development

Research outputs

Bediako Y, Adams R, Reid AJ, Valletta JJ, Ndungu FM, Sodenkamp J, Mwacharo J, Ngoi JM, Kimani D, Kai O, Wambua J, Nyangweso G, de Villiers EP, Sanders M, Lotkowska ME, Lin JW, Manni S, Addy JWG, Recker M, Newbold C, Berriman M, Bejon P, Marsh K, Langhorne J. (2019) *Repeated clinical malaria episodes are associated with modification of the immune system in children*. BMC Med 13;17(1):60. DOI: 10.1186/s12916-019-1292-y
This is one of the first studies to investigate immune responses of children experiencing frequent febrile malaria episodes using systems immunology tools. We identify several immune features that characterise these children, demonstrating the power of such an approach.

Pérez-Mazliah D, Gardner PJ, Schweighoffer E, McLaughlin S, Hosking C, Tumwine I, Davis RS, Potocnik AJ, Tybulewicz VL, Langhorne J. (2018*) Plasmodium-specific atypical memory B cells are short-lived activated B cells.* Elife 7 pii: e39800. DOI: 10.7554/eLife.39800
This paper provides strong evidence that "atypical" B cells are short-lived activated B cells, and are probably the result of chronic stimulation and not the cause of chronic malaria. This questions the commonly held view that atypical B cells are evidence of an aberrant or defective response in malaria.

Brugat, T; Reid, AJ; Lin, J-w; Cunningham, D; Tumwine, I; Kushinga, G; McLaughlin, S; Spence, P; Böhme, U; Sanders, M; Conteh, S; Bushell, E; Metcalf, T; Billker, O; Duffy, PE; Newbold, C; Berriman, M and Langhorne, J (2017) *Antibody-independent mechanisms regulate the establishment of chronic Plasmodium infection*. Nature Microbiology 2, 16276. DOI: 10.1038/nmicrobiol.2016.276
We showed that selection of infected erythrocytes expressing members of the *pir* multigene family is not dependent on antibody. Some *pirs* are associated with virulence of the infection, hinting at other functions of PIR. This is an important paper as it opens up new research avenues on the causes of malaria chronicity and virulence.

Pérez-Mazliah, D; Ng, DHL; Freitas do Rosário, AP; McLaughlin, S; Mastelic-Gavillet, B; Sodenkamp, J; Kushinga, G and Langhorne, J (2015). ***Disruption of IL-21 signaling affects T cell-B cell interactions and abrogates protective humoral immunity to malaria*****. PLOS Pathogens 11, e1004715. DOI: 10.1371/journal.ppat.1004715**
This is the first demonstration of the crucial role of IL-21 from T cells in development of protective immunity to malaria.

Nahrendorf W, Spence PJ, Tumwine I, Lévy P, Jarra W, Sauerwein RW, Langhorne J. (2015) ***Blood-stage immunity to Plasmodium chabaudi malaria following chemoprophylaxis and sporozoite immunization*****. Elife.4:e05165 DOI: 10.7554/eLife.05165**
Immunity to malaria is generally considered to be stage specific; i.e. immunity to blood stages does not protect against exo-erythrocytic stages and vice versa. This view has strongly influenced vaccine development. Here we show that there is a substantial cross-stage immunity. This has important implications for selection of vaccine candidate molecules.