Title of PhD project / theme	**Role of lymphocytes in the pathogenesis of and the protection against cerebral malaria**
Supervisory team	Primary supervisor: Sam Wassmer, PhD. Associate Professor of Immunology Department of Infection Biology Faculty of Infectious and Tropical Diseases LSHTM E-mail: sam.wassmer@lshtm.ac.uk Co-supervisor: Katsuyuki Yui, M.D., PhD. Professor, Department of Immunology School of Medicine, School of Tropical Medicine and Global Health (TMGH) Nagasaki University E-mail: katsu@nagasaki-u.ac.jp Other supervisory team members: Shin-Ichi Inoue, PhD Associate Professor, Department of Immunology School of Medicine, Graduate School of Biomedical Sciences Nagasaki University Email: shinichi@nagasaki-u.ac.jp Kevin Tetteh, Ph.D. Associate Professor Department of Infection Biology Faculty of Infectious and Tropical Diseases LSHTM E-mail: kevin.tetteh@lshtm.ac.uk

Brief description of project / theme	Cerebral malaria (CM) is the most severe complication of *Plasmodium falciparum* infection. Mortality is high, even with appropriate clinical management, and survivors often present neurocognitive sequelae. The physiopathological mechanisms leading to the development of this neurological syndrome remain poorly understood – only a fraction of malaria patients develops severe disease, while the majority show mild symptoms. The resistance to the disease onset is associated with host immune responses obtained by a continuous exposure to *P. falciparum* malaria and explains why children under the age of 5 predominantly develop CM in high endemicity settings. In low endemicity settings like India, the theory is that such resistance fails to be triggered early in life due to inconsistent malaria exposure, resulting in patients developing CM at all ages. Studies suggest that lymphocyte immune responses play crucial roles for the pathogenesis as well as protection against cerebral malaria. However, the underlying cellular and molecular mechanisms are poorly understood. This project is designed to compare the profile of B and T cells between uncomplicated malaria and CM patients in India, with a view to better understanding the immune mechanisms underlying the development of protection against this neurological syndrome and developing novel strategies to prevent its progression in low-endemicity settings. The project will build upon and expand the scope of an ongoing programme grant in Rourkela, Odisha, that aims to decipher the parasite and host factors leading to CM in *P. falciparum* infections. B and T cells will be isolated from our highly characterised cohort of CM patients at Ispat General Hospital before being studied. In addition, brain tissue collected from fatal cases will also be used for the analysis of brain-specific T cells. Using a new cell-based assay developed a LSHTM, antigen-binding profiles of circulating B cells from uncomplicated malaria and CM patients will be assessed and contrasted for the first time. Novel recombinant targets will be printed using a unique on-the-fly microarray printer before profiling B cell binding signatures using a recently developed protocol. In parallel, new assays will be developed to evaluate whether antigens predominately recognised by B cells from patients with CM in our cohort are also dominant antigens for T cells, which potentially mediate the pathogenesis. These T cells will be phenotypically and functionally characterised and contrasted between the two patient groups by analysing both circulating and brain-specific cells. In addition, malaria antigen-specific IL-27-producing $CD4^+$ T cells, which regulate immune response, will be measured in the circulation of patients (Kimura et al, Immunity, 2016). In parallel, $CD8^+$ T cells in the cerebral vasculature of paediatric patients who died of CM will be characterised using multiplexed immunohistochemistry and single-cell transcriptomics.

	Taken together, these approaches will allow a unique and exhaustive characterisation of the immune cell profiles associated with protection from and susceptibility to CM. The PhD student will initially study immune responses to malaria infection using relevant mouse models in Nagasaki to learn basic immunological techniques and investigate mechanisms underlying immune modulation during malaria infection. Later, the student will apply his/her immunological skills to examine B and T cells isolated from uncomplicated malaria vs. CM in a low-endemic setting in India.
The role of LSHTM and NU in this collaborative project	Nagasaki University: The initial training of immunology will be done at Nagasaki University under the supervision of Shin-Ichi Inoue and Katsuyuki Yui using a relevant mouse model of cerebral malaria. The immune response of T cells from patients in India will be examined in collaboration between Nagasaki and LSHTM teams. LSHTM: The candidate will validate results generated in Nagasaki by analysing B and T cells from a highly characterised cohort of patients from India, enrolled as part of an ongoing research project led by Sam Wassmer. For the B cell analysis, the candidate will use a novel array developed by Kevin Tetteh. Some parts of the analysis will be carried out in London, and some others in the field in India.
Particular *prior* educational requirements for a student undertaking this project	A 2:1 BSc degree or equivalent in the Biological Sciences, with basic knowledge of Immunology is required; A MSc degree in Immunology or related field is ideal.
Skills we expect a student to develop/acquire whilst pursuing this project	The candidate will study immunology of severe malaria infection in both laboratory (Nagasaki, London) and field (India) settings. He/She will acquire knowledge of immunology, skills to ask appropriate questions and design methods to solve the questions and problems in both laboratory and fields.