Title of PhD project / theme	**Understanding artemisinin and partner drug susceptibility in *Plasmodium falciparum* : genetic crosses with parasites displaying susceptibility phenotypes to identify new resistance genes**
Supervisory team	**1. Colin Sutherland – LSHTM** **2.** Richard Culleton – Nagasaki University
Brief description of project / theme	Malaria parasites exhibit extensive genetic polymorphism which often leads to phenotypic differences between parasite strains. These can include differences in susceptibility to antimalarial drugs. For example, polymorphisms in the genes *pfubp1*, *pfap2mu*, *pfcoronin* and *pfk13* are all linked to reduced artemisinin susceptibility *in vitro.* This suggests there are multiple ways malaria parasites can evolve reduced susceptibility, and additional, but as yet undescribed genes are very likely to be important. We propose a systematic evaluation of *in vitro* susceptibility to artemisinin and partner drugs of a collection of clinical *P. falciparum* isolates held at LSHTM, using established state-of-the-art semi-automated assay approaches. Parasites with a defined phenotype of interest will then be evaluated for their ability to generate gametocytes and infect mosquitoes. Gametocyte-producing parasite lines with a phenotype of interest will be transferred to Nagasaki University, where genetic crossing with the wild-type NF54 line will be performed. Progeny will be isolated using newly developed humanised mouse methodologies, established in culture, and transported to LSHTM for medium-throughput drug susceptibility phenotyping. All progeny will also be placed into a joint Nagasaki-LSHTM genome sequencing pipeline and the resulting data analysed to identify loci implicated in conferring parental phenotypes, including drug susceptibility, to the progeny of each cross.
The role of LSHTM and NU in this collaborative project	Synergies between the two research groups have already been established; parasite drug susceptibility will be determined at LSHTM in Year 1 -2, and gametocyte production tested for each clinical line. Also, maternally-inherited loci of the apicoplast and mitochondrion will be identified. In Year 2-3, parasite cultures will be shipped to Nagasaki to be crossed with NF54 and passaged through the liver of humanised mice to produce progeny of each cross.

	Progeny will then be phenotyped back at LSHTM, but both sites will contribute to genome sequencing work and data analysis using a joint pipeline partially established in a previous project.
Particular *prior* educational requirements for a student undertaking this project	Prior experience of *in vitro* cell culture would be an advantage. A degree including training in biochemistry or genetics desirable.
Skills we expect a student to develop/acquire whilst pursuing this project	Malaria parasite culture techniques. Manipulation and phenotypic characterisation of malaria parasites *in vitro*. Genetics, genomics, bioinformatics and molecular biology techniques.