Project Details	
Project Code	MRCIIAR24Br Rivino
Title	Identifying immune signatures associated with severe dengue virus infection
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Six billion people will be at risk of dengue virus infections by 2080 and we still lack a cure and effective vaccines for dengue. This multidisciplinary project aims to identify immunological signatures associated with severe dengue, to inform the design of dengue therapies/vaccines. You will achieve this by designing a novel bioinformatic platform that can integrate high-dimensional datasets obtained using cutting-edge immunological techniques in a CL-3 laboratory.
Description	This is an exciting opportunity to work in a multi-disciplinary team of experts in dengue virus immunology/immune signatures, machine-learning for high-dimensional datasets and dengue pathogenesis. Advances in high throughput multi-omics are revolutionizing the immunology field and providing opportunities for data-driven understanding of mechanisms underpinning immune-mediated diseases. However, the lack of appropriate computational methods that allow us to integrate diverse multidimensional datasets, to identify immune signatures associated with clinical outcomes, remains a major hurdle in achieving these goals. Dengue virus (DENV) circulates as four infectious serotypes and infects 390 million people per year. Despite the heavy burden of disease, there is no therapeutic for dengue and two licensed dengue vaccines fail to protect against all DENV serotypes. Severe dengue is associated with secondary infections with a different DENV serotype, and the host immune response is believed to play a role in immunopathology. However, the mechanisms underlying the progression to severe dengue remain unclear. Data from our laboratories suggest that impairment of the anti-viral functions of CD8+T and NK cells plays a central role in the development of severe dengue. Our teams have generated a large immunological, unpublished dataset from the analysis of blood samples from a dengue patient cohort in Vietnam (~200 patients) which includes high dimensional phenotypic/functional flow cytometry data, metabolic activity, single cell transcriptomics, soluble biomarker data (cytokines/chemokines, inflammatory/vascular markers) and detailed longitudinal clinical assessments. The integration of these diverse datasets to inform disease mechanisms remains a large challenge in the field. Aim and objectives: The overarching aim of this project is to identify the immunological mechanisms underlying severe disease in dengue. This will be achieved through 2 broad objectives: (1) To design a novel bioinformatic platform that allows us to integrate these diverse datasets and identify associations between immune signatures and disease outcomes. The designed platform, which will perform analyses using state-of-the-art machine learning methodologies for high-dimensional datasets, will also be valuable for future studies in other diseases beyond dengue. This aim will be supported by a machine learning expert specialized in high-dimensional data (Artemiou) and an expert in disease-specific immune fingerprints (Eberl) in Cardiff. (2) To uncover the biological

	mechanisms underlying the associations with severe disease identified in objective 1. The student will use state-of-the-art immunological/cellular assays to validate the signals identified in objective 1 and investigate the mechanisms underlying the associations between immune profiles and disease severity. We will use established techniques in the lab, as well as design novel assays, to address the interplay between different immune cells in peripheral blood mononuclear cells/serum samples from dengue patients (from the same dengue cohort as in objective 1, and from other available dengue cohorts from Vietnam). This aim will be supported by the Rivino (Bristol) and Yacoub (Vietnam) teams which have extensive expertise in the immunology and pathogenesis of dengue. The student will lead the design of the bioinformatic platform and acquire skills in cutting-edge immunological techniques, with support from experts in the fields. Development of both laboratory and bioinformatic skills are key to the success of this multidisciplinary project. The student will have opportunities to read the literature and propose ideas to steer the experiments for the second objective of the project, aimed at identifying mechanisms underlying severe dengue. Requirements: Mandatory: basic programming skills. Desirable: advanced programming skills.
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Lead Supervisor	
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