Project Details	
Project Code	MRC23IIARCa Eberl
Title	Novel tools for analysis of high-dimensional cytometry data: implications for patients with severe dengue
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	Cytometry - the method of identifying and counting cells - is a cornerstone of biomedical research and clinical practice. Cytometry generates massive datasets too unwieldy to manage efficiently, thereby slowing down scientific progress. We aim to empower scientists to analyse and interpret complex data at a quality, speed and reproducibility never seen before, by developing novel mathematical approaches and apply them to immune profiles of dengue patients.
Description	BACKGROUND Cytometry has become a cornerstone to biomedical research and clinical diagnosis. In many health conditions, the understanding of pathological mechanisms and how to exploit them for patient benefit relies entirely on cytometry. In response to technological advances, the domain of 'cytometry bioinformatics' is rapidly evolving to provide new computational solutions for analysis and presentation of complex datasets generated by flow and mass cytometry, including autonomous gating, supervised classification, dimension reduction and unsupervised clustering. SIGNIFICANCE Existing algorithms for cytometry analysis can only handle a fraction of the available dataset and are limited to few options, thereby biasing outputs, compromising reliability and ultimately slowing scientific progress. We aim to empower researchers to visualise and interpret cytometry datasets through new mathematical tools and a uniquely versatile, bespoke software ('CytoPy'), at a quality, speed and reproducibility never seen before. To our knowledge, no other commercial or open-source solution is capable of delivering state-of-the-art methods in a similarly user-friendly but powerful 'all-in-one' framework. KEY AIMS 1) Create novel dimension reduction approaches for dimension reduction and visualisation of high-dimensional data overcoming performance limitations of existing methods 2) Pioneer ensemble clustering techniques and improve the overall computational performance of cytometry analysis 3) Validate novel algorithms in real-world cohorts of immediate relevance for health and disease, make novel observations from existing and ongoing studies, and generate new hypotheses RESEARCH PLAN The student will develop novel technologies for dimension reduction and visualisation without loss of information as in current methods that depend on data down-sampling. They will implement consensus methods that scale to large datasets, using heuristic ways of ensemble clustering with specific application to cytometry, and benchmark this work against existing datasets and clustering solutions. Together, this will represent the most versatile, powerful and unbiased analysis platform to date, and be of immediate interest to basic, applied and clinical cytometry users for immunophenotyping, biomarker discovery and identification of disease subtypes. The student will validate these algorithms in real-world datasets with a view to identifying immune signatures related to protection and/or immunopathology during dengue infection. While earlier studies have identified roles for antibodies in the immunopathology the contribution of T cells and NK cells remains

	unclear. Unpublished and published data from our team suggest that NK cell impairment underlies severe infection and that dengue-specific T cells express exhaustion markers such as PD-1. The student will have access to datasets from completed studies (performed at Duke-NUS, Singapore), and will participate in ongoing immune profiling studies in the Rivino lab, in collaboration with Dr Sophie Yacoub (OUCRU, Vietnam). PREVIOUS WORK Prof Eberl and Dr Artemiou recently published a preliminary version of CytoPy, a new software that facilitates rapid integration and application of novel algorithms for high-dimensional cytometry data. The solutions from the present project will be applied to completed and ongoing studies in dengue patients. Dr Rivino has already collected flow cytometry (18-colour panels) and RNAseq data of T, NK, B cells and monocytes from 69 dengue patients and identified a signature linked with dengue severity. Ongoing work aims to characterise the underlying mechanism, by analysing dengue patients with standard BMI or overweight/obesity (n=150), as well as patients who receive metformin as host-directed therapeutic (n=60), including phenotype and function of T, NK and B cells longitudinally, and changes in serum biomarkers between hospital admission and discharge.
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