Spatially resolved cell atlas of the bone marrow and spleen reveal marked heterogeneity in tissue reorganization in fatal *P. vivax* infection

Joao Luiz Silva-Filho[1,2], Kevin Couper[6], Marcus VG Lacerda[4,5], Fabio TM Costa[3], Matthias Marti[1,2]

1. *University of Glasgow, Glasgow, SCOTLAND, United Kingdom*
2. *Vetsuisse and Medical Faculties, University of Zurich, Zurich, Switzerland*
3. *Department of Genetics, Evolution, Microbiology and Immunology, University of Campinas, Campinas, Brazil*
4. *Tropical Medicine Foundation Dr. Heitor Vieira Dourado, Manaus, Brazil*
5. *Institute Leônidas & Maria Deane, Fiocruz, Manaus, Brazil*
6. *University of Manchester, Manchester, United Kingdom*

P. vivax (Pv) infection can cause severe clinical outcomes despite low blood parasitaemia, with a “hidden” parasite population in organs such as the bone marrow (BM) and spleen. This study aims to characterize perturbations induced by Pv infection in BM and spleen and their role in disease pathogenesis by creating a spatially resolved cell atlas in fatal Pv. We analyzed BM (n=3) and spleen (n=5) samples from acute fatal Pv and non-malarial cases using Imaging Mass Cytometry (IMC) and spatial transcriptomics (CoSMx) integrated to H&E. In both organs, we identified cell types and states including infected RBCs (iRBCs) and tracked their maturation. Tissue niches and alterations linked to specific host responses revealed unique features of BM and spleen architecture and marked heterogeneity in tissue reorganization across cases. In two patients, IMC showed iRBCs interacting with activated neutrophils and macrophages and correlating with reduced parasite biomass. Parallel CoSMx analysis revealed strong activation of innate immune responses, antigen (Ag) processing and presentation along with activation of cytokine signaling. These patients died from acute respiratory distress, which may be linked to the myeloid- and T lymphoid-driven antiparasitic response in BM. The third patient had high parasite biomass, with Pv-iRBCs mostly interacting with each other and uninfected RBCs. Transcriptomic analyses showed reduced Ag processing and presentation and suppressed T-cell responses. The higher parasite biomass in this BM sample may be due to parasite evasion, possibly related to a local immune deficient response. Thus, BM responses are associated with different disease trajectories leading to fatal outcome. Ongoing spatial omics of the spleen in fatal Pv infection will be presented. This study underscores the need to examine the impact Pv infection in deep tissues, enhancing our understanding of Pv biology and pathogenesis to reduce malaria burden.