SYSTEMS BIOLOGY OF TYPHOID FEVER: UNRAVELLING REGULATION OF HUMAN HOST-RESPONSES TO INFECTION WITH *SALMONELLA TYPHI* AND LIVE ORAL VACCINATION

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ABOUT THE PROJECT

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Infectious diseases caused by enteric pathogens are endemic specifically in developing countries, and are responsible for several thousands of deaths every year. This proposal will focus on enteric fever caused by Salmonella Typhi and Paratyphi as a model for intestinal infections. Typhoid fever significantly affects South America, sub-Saharan Africa and South-East Asia with approximately>22 million new infections resulting in a 1% fatality rate annually. Control of the disease is hindered due to insufficient understanding of disease pathogenesis and immune responses to the infection, inaccurate diagnostic tests and poor efficacy of licensed vaccines. Thus understanding human host-responses to enteric infections is pivotal in developing improved diagnostic tests and vaccines. The Oxford Vaccine Group (OVG) has recently developed a human challenge model for S. Typhi and Paratyphi. This model was subsequently used to test vaccine efficacy by vaccinating participants prior to ingestion of the bacteria. Systems biology/vaccinology is an interdisciplinary field that combines systems-wide measurements, networks, and predictive modelling in the context of biology, vaccines and infectious disease. Particularly important in this context are regulatory mechanisms, which consist of complex networks involving multiple transcriptional and genetic components. Recently, it has become clear that long non-coding RNAs (lncRNAs) play a pivotal role in the regulation of biological processes by a diverse range of mechanisms. Applying systems biology to samples derived from these unique and highly controlled clinical trials allows us to directly investigate human responses to enteric infections and vaccination. In this proposal, we will specifically address the following three aims: (1) Identifying signatures predictive of vaccine-conferred protection; (2) Identifying diagnostic signatures; (3) Assessing the role of lncRNAs in enteric infection and vaccination. We propose to build a long-lasting partnership between the University of São Paulo and University of Oxford by performing state-of-the-art applied systems biology on samples derived from clinical trials in Oxford and the field, complemented with clinical and immunological/biological data.