Mapping *in situ* immune microenvironments from skin lesions of early controlled human challenge to chronic field infections using spatial transcriptomics

Lead Supervisor: Dr. Nidhi S. Dey
Department: Department of Biology, HYMS, University of York
Email: nidhi.dey@york.ac.uk

Context and Overarching Goals

Cutaneous leishmaniasis is a spectrum of skin parasitic diseases driven by heterogeneous chronic inflammatory responses varying across *Leishmania* species and geographic regions. Human challenge models where volunteers are infected under controlled conditions are a powerful but under validated tool for drug and vaccine development. Our laboratory has generated spatial Visium transcriptomics datasets spanning controlled human challenge infections (*L. major*) and natural field lesions from Ethiopian, Indian, Sri Lankan, and Brazilian patients, creating an unprecedented comparative resource to evaluate how challenge models recapitulate real-world disease.

This project will compare immune microenvironments between challenge and field infections and develop a publicly accessible community resource. The student will: (1) perform comparative spatial transcriptomics analysis to identify conserved immune tissue programs across challenge and field lesions; (2) conduct pathway enrichment analysis to define core versus tissue domain-specific inflammatory modules across *Leishmania* species and disease presentations. (3) perform cellular deconvolution followed by trajectory analysis to examine shifts in immune cell lineages between early and chronic infection; (4) conduct spatially resolved cell-cell communication analysis to map ligand-receptor interaction networks within lesion microenvironments across cohorts; and (5) develop an interactive R Shiny web application providing open access to spatial gene expression data for the global research community.

Expected outcomes include validating human challenge models as representatives of field disease and creating a publicly accessible spatial transcriptomics resource that will accelerate global leishmaniasis research. The student will gain expertise in human immunology, spatial transcriptomics analysis, and web application development, contributing to a community resource that will accelerate global leishmaniasis research.

Computational Aspects and Why HPC is Key

Initial Visium dataset processing — normalisation, dimensionality reduction, and spatially-variable gene identification — has largely been completed, though HPC resources may be required should re-parameterisation be needed. The primary computational demand lies in cellular deconvolution, trajectory analysis on deconvolved populations, and spatially resolved cell-cell communication inference (NicheNet/CellChat), all of which are highly parallelisable but memory-intensive when scaled across four geographically distinct cohorts and multiple species simultaneously. Cross-cohort integration and pathway enrichment analyses further compound this demand. HPC infrastructure (Bede) is essential to the feasibility, scale, and reproducibility of this project.