PI profile

## Stephen Sansom

|  |  |
| --- | --- |
| A person wearing glasses  Description automatically generated with medium confidence | **Associate Professor Stephen Sansom**  **Titles:** Group Leader in Computational and Single Cell Genomics; Innovation PI  **Location:** Kennedy Institute for Rheumatology  **Department:** NDORMs  **Group:** Sansom  **Webpage:** <https://sansomlab.org>  **Email:** stephen.sansom@kennedy.ox.ac.uk |

### GMS themes:

[Please retain any that describe your research, deleting others:]

* Genomic and –omic technologies
* Functional genomics
* Genomics of disease
* Genomic analysis (bioinformatics and statistical genetics)
* From genes to clinic (target discovery, structural biology, medicinal chemistry)
* Application of genomics in the clinic (diagnostics and therapeutics)

### Research Overview

The causes of immune-mediated inflammatory disease (IMIDs) are incompletely understood, but can include genetic factors, lifestyle factors, environmental factors and microbiome composition. Our research is based on the concept that such factors integrate at the cellular level, where they manifest in the form of pathogenic cellular phenotypes and signalling circuits in specific tissues. We use unbiased single cell and spatial genomics approaches to discover problematic cellular phenotypes and signalling circuits directly from patient biopsy samples. By doing so, we aim to understand the molecular and cellular basis of inflammatory disease and to enable the identification and prioritisation of novel targets for therapeutic intervention. Currently, the group has a focus on understanding the pathogenesis of inflammatory bowel disease and HLA-B\*27 ankylosing spondylitis.

### Research Interests

* The pathogenesis of inflammatory bowel disease (IBD) is complex and multifactorial in nature. Recently, in proof-of-concept studies, we combined network and single-cell approaches to explore previously unknown heterogeneity in tissue pathotypes. A more complete understanding of the spectrum of cellular pathotypes that underly IBD will provide a rational basis for the development of novel and personalised treatments. In work recently funded by a 5-year MRC programme grant we are working with the group of Prof. Fiona Powrie, clinical scientists, mucosal immunologists and microbiome specialists to establish a comprehensive atlas of IBD pathotypes and their relationship with disease outcomes.
* Why is the MHC class I molecule HLA-B\*27 linked with inflammatory disease? Spondyloarthritis is a common disease for which the cellular causes remain mysterious despite an extraordinarily strong genetic association with HLA-B\*27 (odds ratio=131). We are using single-cell and spatial genomics data from human patients to evaluate three competing biological hypotheses of how this molecule might act to initiate disease (the arthritogenic peptide hypothesis, the ER stress hypothesis and the free-heavy chain hypothesis).
* The development of new computational pipelines and tools for single-cell and spatial genomics data analysis.

Project areas: Immunology, development, immune-mediated inflammatory disease, inflammation, single-cell genomics, functional genomics, cell-cell interactions, human cell atlas, computational biology

### Specific project proposals:

Please contact directly for further information

*These pages were reviewed/updated:* ***27/09/2022***

### Specific project proposals:

Please contact directly for further information.

Project proposal

# **Title**: **Projects in** **Infectious and autoimmune-related disease**

Supervisors: Stephen Sansom, Paul Bowness

Wet/dry lab mix (approx): 20% wet lab, 80% dry lab

### Description:

Our research involves the generation and analysis of bulk, multi-modal single-cell and spatial genomics datasets from human patients. For data generation, the group has the 10x Chromium and BD rhapsody single cell and the nanoString GeoMx spatial transcriptomics platforms. We are expecting delivery of the higher-resolution nanoString CosMx spatial transcriptomics platform later this year.

Currently, we have opportunities for computational projects in two areas:

1. Network analysis of cellular pathotypes in inflammatory bowel disease. In our initial studies we applied weighted gene co-expression (WGCNA) to bulk RNA-seq profiles from ~100 patients. In this project, you will use more advanced kernel clustering, modularity optimisation and random walk-based algorithms to perform network module identification using a larger RNA-seq dataset from ~1000 patients (IBD Plexus cohorts). The initial goal of the project will be to compare the ability of the algorithms to recover known heterogeneity. The best approach(es) will then be taken forward for novel pathotype discovery. The project will also involve the analysis of single-cell datasets for cell type deconvolution. Discovered pathotypes will be further investigated using spatial transcriptomics and experimental approaches in mouse models. The project will be performed in close collaboration with the group of Professor Fiona Powrie and the wider MRC project team.
2. Investigating the role of HLA-B\*27 in ankylosing spondylitis. Ankylosing spondylitis is a common form of arthritis for which the cellular causes remain mysterious despite a remarkably strong genetic association with HLA-B\*27 (odds ratio=131). Projects in this area will use single-cell and spatial genomics data from human patients to evaluate three competing biological hypotheses of how HLA-B\*27 might act to initiate disease (the arthritogenic peptide hypothesis, the ER stress hypothesis and the free-heavy chain hypothesis). This work will involve the modelling of cell-cell interactions and the integration of spatial and genetic data. It will be co-supervised by Prof Paul Bowness.

### Training Opportunities:

You will learn how to use network approaches to model large transcriptomics dataset and to analyse and interpret single-cell genomics data. This will involve writing bioinformatics pipelines in Python, performing statistical analysis and data visualisation in R and the use of high-performance compute clusters. You will have the opportunity to work closely with wet-lab and clinical colleagues.

### Background reading / references:

* IL-1-driven stromal-neutrophil interaction in deep ulcers defines a pathotype of therapy non-responsive inflammatory bowel disease. Friedrich M. et al. Nature Medicine. 2021
* Deconvolution of monocyte responses in inflammatory bowel disease reveals an IL-1 cytokine network that regulates IL-23 in genetic and acquired IL-10 resistance. Aschenbrenner D et al. Gut, 2020.
* IRF5 guides monocytes toward an inflammatory CD11c+ macrophage phenotype and promotes intestinal inflammation. Alastair L Corbin, et. al. Science Immunology, 2020.
* Distinct fibroblast subsets drive inflammation and damage in arthritis. Adam P. Croft, et. al. Nature, 2019
* Progress in our understanding of the pathogenesis of ankylosing spondylitis. Simone D, Al Mossawi and Bowness P. Rheumatology (Oxford), 2018