# MSc Bioinformatics and Computational Biology programme

# Research Project Proposal

**Examining the JAK/STAT signalling pathway in intestinal epithelial cells and macrophages in publicly available RNASeq datasets from Inflammatory Bowel Disease**

Inflammatory bowel disease (IBD) is typically classified as either ulcerative colitis (UC) or Crohn’s disease (CD) and characterized by chronic inflammation of the gastrointestinal tract. Although its aetiology is unknown, the impact of gut microbiota and genetic, inflammatory, and environmental factors has been described as contributors to the disease (Friedrich, Pohin, Powrie 2019). Crohn’s disease has become a global disease, being a lifelong condition with a high burden to both patients and public health. CD is clinically stratified by location with distinct differences in presentation and risk for progression (Dulai et al., 2019). Ileal CD, compared to colonic CD, poses a higher risk for delayed diagnosis and potential complications. Its different immune response profile makes it an essential target for new treatment strategies. Phase III clinical trials have shown that treatment with oral Janus Kinase (JAK) inhibitors can alleviate disease in patients with CD. However, these inhibitors are associated with certain side effects, including the risk of cardiovascular problems.

The JAK1/2-STAT1 intra-cellular signalling pathway is activated by the Th1 cytokine IFNg alone or in synergy with another Th1 cytokine, TNFa. The pathway drives the expression of inflammatory genes in multiple cell types, typically characteristic of active or inflamed CD (Salas et al., 2020). This pathway is tightly regulated by the Suppressor of Cytokine Signaling 1 (SOCS1) protein, which prevents excessive or prolonged immune activation. Dysregulation of the JAK-STAT pathway and SOCS1 has been implicated in various immune-mediated diseases, including CD (Rodari et al., 2023). In addition, the pathway has been shown to induce cell death in intestinal epithelial cells in response to Th1 cytokines (Woznicki et al., 2021). The expression of the JAK/STAT pathway genes in gut cells from CD at different locations has not been examined previously.

This project aims to investigate the expression of JAK/STAT/SOCS1 genes from CD patients and healthy controls at different locations, disease stage and cell subset. For this purpose, publicly available single-cell RNA-seq datasets will be utilised to identify genes and pathways influenced by JAK-STAT pathway activation in the context of disease stage, location and cell type. Findings from this study will enhance our understanding of the JAK-STAT pathway and CD.

**Objectives:**

1. Identify differentially expressed genes (DEGs) in the JAK-STAT pathway in CD patients versus healthy controls using single-cell RNA-seq data analysis using publicly available data sets.
2. Compare expression levels in different cell types (epithelial cell and macrophages), disease stage (active vs inactive) and locations of the human GI tract (small intestine vs colon) with a focus on characteristics of the ileum.
3. Elucidate the effect of JAK/STAT/SCOS1 pathway activation on barrier function, epigenetic modifications, autophagy and protein interactions in CD.

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