Title: Understanding immune-parenchymal cell interactions in active and refractory coeliac disease through spatial analysis approaches

Summary:

Coeliac disease occurs when gluten triggers the gut's immune system, leading to troublesome symptoms for some patients. Sometimes the inflammation continues even after gluten removal (refractory coeliac disease type 1), and can develop into refractory coeliac disease type 2, which can lead to cancer. The only treatment for coeliac disease is a strict, lifelong gluten free diet, while treatments for refractory coeliac disease type 1 and refractory coeliac disease type 2 are limited and often ineffective.

Recently we studied what single cells in the gut are doing in coeliac disease using single-cell gene sequencing. This has shown several different types of cells that are profoundly altered in coeliac disease, and suggested potential interactions between cells, including gluten-specific immune cells such as helper T-cells, killer T-cells and antibody-producing B-cells, and different epithelial (gut lining) cells. However, we don't know how these immunological 'jigsaw pieces' fit together.

One key unknown is where these different cells are precisely located in the gut, who their neighbours are, and how they might be interacting. We believe that the cell types involved in coeliac disease form functional 'units' of different cell types arranged close together in the gut, interacting in specific ways. This project will help solve the spatial coeliac 'jigsaw' by working out where the key pieces are found.

First, we will study where different cell types are located in the gut in coeliac disease. We have performed pilot experiments using techniques which let us look at exactly where genes and cell types are found in the gut, called spatial transcriptomics. This allows us to pinpoint which cells are where, and who they are talking to. Second, we will apply these methods to the dynamic state of a gluten challenge in coeliac disease. This allows us to see what cells are doing right at the time of gluten exposure – the cells actually driving the disease. Third, we will apply these novel approaches to refractory coeliac disease type 1 and refractory coeliac disease type 2. We will perform single-cell sequencing and spatial transcriptomics to better to understand how refractory coeliac disease type 1 differs from active coeliac disease, and which cell types express the mutations seen in refractory coeliac disease type 2.

Our team has the clinical, immunological, and informatic expertise to deliver this project, including an exciting collaboration with one of the two national refractory coeliac disease centres. We have performed pilot work showing this plan is feasible. This project will increase our understanding of where the pieces of the immunological jigsaw are found, which cause inflammation and the symptoms patients face. It may identify targets for treatment, the triggers for coeliac disease, and strategies to help with refractory coeliac disease.

Title: Characterising antibody responses to the gut microbiota in adult coeliac disease

Summary:

The human body is host to trillions of microorganisms such as bacteria, viruses and fungi. The largest population of microorganisms within the body resides in the intestine and is collectively called the gut microbiota. Bacteria within the gut microbiota have been shown to exert an important role in maintaining human health, such that disturbances in the composition and/or function of the bacteria can lead to adverse health outcomes. Studies have also implied that changes in gut bacteria might impact the development of coeliac disease. However, trying to identify which specific bacteria affect disease development and/or progression is a major challenge and is currently unclear.

The body contains specialised immune cells, called plasma cells, which produce antibodies, such as immunoglobulin A (IgA), that bind to microorganisms to help prevent infection and maintain a diverse community of gut bacteria. Previous work has shown that identifying the specific bacteria that are bound by IgA, and other antibody subtypes, in conditions such as inflammatory bowel disease and diabetes can help identify strains that impact disease susceptibility and severity. Therefore, we aim to characterise IgA/antibody responses to gut bacteria in active coeliac disease, to identify disease-relevant bacteria.

To do this, we will sample the gut microbiota from the intestines of patients with active coeliac disease, patients with inactive (treated) coeliac disease, and from non-coeliac controls. We will then separate bacteria into IgA-bound and IgA-unbound fractions and identify which bacterial strains are present in each group using a high-throughput sequencing technique. In addition, we will evaluate binding of antibodies present in blood and stool of the same patients to cultured human gut bacteria strains that are normally present within gut microbiota. We will then evaluate the specific gut commensal antibody responses in the context of disease-relevant clinical information.

Together, we envisage these data will help identify gut bacteria that interact with the immune system in coeliac disease, and thus may impact disease development and/or progression, as well as help with the identification of novel non-invasive disease biomarkers. We aim to disseminate our findings to interested clinical, academic and commercial parties, as well as patients and the public, through attendance at a range of conferences and workshops towards the end of the project timeline.