Department of Pathology fully-funded PhD studentships: project proposal form

Division	Cellular and Molecular Pathology
Supervisor	Dr Elizabeth Soilleux
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	Development of a high throughput butyrophilin analysis, to complement a holistic immunological analysis tool for clinical diagnosis/prediction of prognosis
Project abstract for advert (Max 100 words)	working with Nonacus Ltd, we developed a high throughput capture-based analytical tool for T-cell and B-cell receptor repertoire and HLA typing, which we are validating for diagnosis of immune/ inflammatory conditions (e.g., coeliac disease and inflammatory bowel disease) and testing as a predictor of cancer prognosis and/ or response to immunomodulatory therapy. Our capture/ analytical pipeline includes HLA typing because it impacts upon the alpha/beta T-cell receptor repertoire. We now wish to develop a capture-based system for butyrophilin analysis to add to our clinical pipeline, in view of the importance of the highly polymorphic butyrophilin system in modulating gamma/delta T-cell function.
Keywords Please provide up to five	T-cell receptor repertoire Butyrophilin Clinical diagnosis Immunomodulation Cancer
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Working with Nonacus Ltd with Coeliac UK/ Innovate UK and MRC funding, we have developed a high throughput capture-based sequencing tool for T-cell and B-cell receptor repertoire, together with a bioinformatic algorithm, which can be used to diagnose immune/ inflammatory conditions (e.g., coeliac disease and inflammatory bowel disease) in patient biopsy samples, as an alternative to biopsy examination under the microscope. We are also testing our pipeline as an early diagnostic test for cancer and lymphoma and as a predictor of cancer prognosis and/ or response to immunomodulatory therapy. Because T-cells recognise antigens in the context of a particular HLA type, we include HLA typing in our capture/ analytical pipeline. For coeliac disease, for example, which is tightly associated with HLA-DQ2/8, this is very important diagnostically. As we expand this clinical diagnostic/ predictive approach to more conditions, we recognise the utility of interrogating additional analogous immune loci, in particular the highly polymorphic butyrophilin system, which is important in modulating gamma/delta T-cell function. Recent data shows a lack of expression of a butyrophilin family member, BTNL8, in small intestine in coeliac disease, a

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	condition driven by gamma/delta T-cells, and the exact mechanisms controlling this loss of expression remain unclear. We now wish to develop a capture-based system for butyrophilin analysis to add to our pipeline. We will initially use this to determine the association of butyrophilin family polymorphisms/ deletions with various pathologies, aiming to develop new clinical assays for diagnosis and prediction of prognosis in immunologically mediated/ modulated conditions.
Three of your most important publications in support of the proposed project	Roberts, T., Huang, Y., Bibawi, H., Matharu, B., Bench, A., Scott, M., Liu, H. Contribution of immunoglobulin lambda light chain gene rearrangement analysis in the diagnosis of lymphoproliferative disorders. British Journal of Haematology (2019) 185(2):261-265. 2. Colling, R., Wang, L.M., Soilleux, E. Validating a fully automated real-time PCR based system for use in the molecular diagnostic analysis of colorectal carcinoma: a comparison with NGS and IHC. Journal of Clinical Pathology. (2017) 70(7):610-614. 3. Colling R., Royston, D., Soilleux E. The role of clonality studies in diagnostic molecular haematopathology. Journal of Hematopathology. (2016) 8;9(3):143-147