Project Details	
Project Code	MRCIIAR26Ex Cano-Gamez
Title	Decoding Lupus: using liquid biopsies to understand autoimmunity
Research Theme	IIAR
Project Type	Mixed (50% wet lab, 50% dry lab)
Summary	Lupus is a serious autoimmune disease where the immune system attacks the body's own cells. An important feature of lupus is the buildup of cell-free DNA (cfDNA) —fragments of dying cells that are not properly disposed of and accumulate in the bloodstream. This project will use liquid biopsies and next generation sequencing to analyse cfDNA from lupus patients. By studying cfDNA fragmentation, sequence, and molecular characteristics, we aim to train machine learning models to predict disease risk and severity. This project blends genomics and data science to offer new insights and improve how we understand and monitor this disease.
Description	**Background** Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc) are devastating medical conditions which affect as many as one in ten individuals. They cause significant distress and are challenging to treat. These conditions are caused by the immune system reacting to and mounting an aggressive response to the body's own cells and tissues, which are usually harmless. Autoimmune reactions result in generalised and uncontrolled inflammation, which can lead to organ dysfunction and put patients at risk of complications and ill health. An important characteristic of autoimmune diseases is that patients can present with autoantibodies against DNA, histones, and other internal structures usually found only within cells. It is unclear how the immune system comes to encounter these molecules and why it reacts against them. It has been proposed that this may relate to impaired removal of cells after they die. During apoptosis, the DNA of dying cells is released into the circulation, where it is detectable as circulating cell-free DNA (cfDNA). This material is usually rapidly cleared by the liver and kidney. However, in autoimmune diseases this process may be impaired, as illustrated by patients with monogenic forms of lupus who carry mutations in genes involved in clearing cfDNA (e.g. the DNASE1L3 enzyme). If clearance of cfDNA is impaired in lupus, then one would expect cfDNA to carry vital information about disease which could be harnessed to better understand the alterations present in each patient and inform their clinical care. Indeed, recent studies have shown that lupus patients show differences in their cfDNA, such as signs of abnormal cleavage, shorter molecules, and different methylation patterns. If properly understood, this information could be exploited to develop novel diagnostics, paving the way for precision medicine. Importantly, cfDNA can be recovered from a minimally invasive blood sample (i.e. a "liquid biopsy"), making it particularly promising for the development of novel diagnostics. This project aims to advance precision medicine in autoimmune diseases by combining cutting-edge next generation sequencing (NGS) technologies and data science to study cfDNA in lupus patients. This will

	help us understand which cfDNA characteristics underlie different features of disease, such as the levels of different autoantibodies and the risk of disease complications. **Project aims** • To understand how cfDNA differs between lupus patients and healthy controls • To pinpoint cfDNA characteristics associated with disease severity (i.e. candidate biomarkers) • To understand if cfDNA alterations lead to the production of autoantibodies • To train machine learning models for risk stratification and precision medicine based on liquid biopsies • To identify routes for clinical translation, maximising patient benefit **Proposed project structure** The student will first conduct a review of existing literature on cfDNA characteristics and lupus. This will enable them to understand which cfDNA features are most likely to be clinically relevant and informative for biomarker discovery. The student will discuss with their supervisory team how these characteristics can best be measured in patients using omics technologies. For example, the student may decide to employ techniques like Nanopore-based sequencing or enzymatic DNA methylation sequencing (EM-seq), amongst others. The student will also identify the most suitable computational and statistical approaches to analyse the resulting data, including how features may best be used for machine learning applications. During the first half of the project, the student will conduct experimental work to isolate and quality assess cfDNA from plasma samples collected from healthy volunteers and lupus patients. The student will sequence these samples using their methodology of choice, generating a comprehensive high-throughput data set of cfDNA in lupus. During the second half of the project, the student will conduct computational work to process and interpret these data using a high-performance computing infrastructure. They will integrate the information derived from their experiments with clinical data from patient health records to understand the processes underlying lupus. For example, they may employ statistical techniques like mediation analysis to assess if cfDNA is causally linked to the production of different autoantibodies. Finally, the student will train machine learning models on a wide array of cfDNA features with the aim of developing new tools to stratify patients by clinical risk. Anticipated project impact By discussing their results with their supervisory team, clinicians, rheumatology consultants, and patient and participant involvement (PPI) groups, the student will identify potential routes for future translation of their findings, bringing us a step closer to achieving precision medicine for autoimmune disorders.
Supervisory Team	
Lead Supervisor	
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