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Department Name	Infection, Immunity and Inflammation
Supervisors (2 Max) Include email addresses	Dr Athanasios Didangelos and Professor Jon Barratt Ad482@leicester.ac.uk and jb81@leicester.ac.uk
Funding Status	Competition Funded Project (European Students Only)
Application Deadline date	6/4/18
Project Title	Using state-of-the-art proteomics to study the cellular and extracellular protein composition in human kidney disease; identification of novel biomarkers and bioactive drug targets in IgA Nephropathy.
Project Description (max 700 words)	One of the key pathological characteristics of IgA nephropathy (IgAN) is the maladaptive and chronic accumulation and remodelling of the extracellular matrix (ECM) in affected glomeruli leading to fibrosis and progressive loss of function. Despite that, the composition, cellular metabolism and functional properties of the matrix and the fibrotic response in IgAN have not received much attention. In addition, little is know about the inflammatory mechanisms that drive fibroproliferative changes in affected kidneys. In this mechanistic and translational PhD project we will utilise innovative proteomics, bioinformatics and cell biology workflows to characterise and quantify for the first time the cellular and extracellular proteome in human IgAN pathology using advanced mass-spectrometry (LC-MS/MS) and computational approaches. We will focus on inflammatory and fibrotic mechanisms. The PhD project has 3 key objectives: **Objective 1**. Achieve accurate quantitation and maximize the number of identified cellular and extracellular tissue proteins with unknown function and therapeutic potential in IgAN. We will focus on proteins with inflammatory and fibrotic function. To do this the student will use innovative biochemical tissue protein fractionation methods on clinical specimens followed by ultrahigh-resolution quantitative proteomics. Apart from mapping the kidney tissue proteome for the first time, we anticipate to identify highly differentially regulated proteins with soluble inflammatory and fibrotic bioactivity for further mechanistic and drug-targeting studies (see below) as well as biomarker potential for detection in patient serum. In addition, using novel degradomics approaches, we will try to identify soluble proteolytic products that could be detected in clinical urine samples as disease biomarkers. **Objective 2**. Identify and target novel mechanistic and therapeutic

	molecules using advanced computational approaches. More specifically, we will carefully filter the high-throughput proteomics datasets derived from **Objective 1** to identify top differentially regulated mechanistic and therapeutic (druggable) candidates by utilising bioinformatics tools developed in our lab, including systems-wide protein-protein and protein-drug interaction network analysis approaches, databases and prediction algorithms. Here we want to isolate the best candidates based on novelty, mechanistic and drug-targeting potential for kidney disease for further *in vitro* and *in vivo* studies (see **Objective 3**). We will focus on soluble proteins with novel inflammatory and fibrotic bioactivity. **Objective 3**. Mechanistic, drug-targeting and biomarker studies. Here, the student will apply the key findings from **Objectives 1** & **2** in cell and tissue models of human IgAN. In more detail, functionally important proteins or protein clusters will be quantitatively and qualitatively validated using a variety of methods (qPCR, ELISA, immunoblotting, state-of-the-art tissue micro-cytometry). The most promising candidates will be then examined for potential disease-modifying bioactivity using cell and tissue biology approaches with drugs, inhibitors and siRNA (RNAi) blocking approaches. We expect to target novel inflammatory and fibrotic proteins. In summary, the student will comprehensively characterise the IgAN cellular and extracellular proteome and will map pathological tissue remodelling for the first time. Our goal is to develop the most extensive quantitative library of IgAN protein expression and to identify cellular (inflammatory) and extracellular (fibrotic) proteins with disease-modifying bioactivity and biomarker potential. The student will benefit from a variety of state-of-the-art techniques ranging from tissue proteomics and bioinformatics to micro-cytometry and classic cell biology and biochemistry.
References	**Dr Didangelos publications**: All publications: https://www.ncbi.nlm.nih.gov/pubmed/?term=didangelos+a GoogleScholar: https://scholar.google.co.uk/citations?user=9scnC-IAAAAJ
Funding Information	3 Year CLS Funded Studentship. Funding provides UK/EU fee waiver and Stipend at UK Research Council rates for 3 years. Available to UK/EU applicants only
Link to online Application web page	https://www2.le.ac.uk/research-degrees/how-to-apply/online
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