Division (delete as appropriate): Biomedical Sciences

<table>
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<th>Project Title:</th>
<th>The Role of Protein-Carbohydrate Interactions in Regulating Haemostasis</th>
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<tr>
<td>Degree (delete as appropriate):</td>
<td>PhD</td>
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<td>Mode of Study (delete as appropriate):</td>
<td>Full time</td>
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<td>Project suitability (delete as appropriate):</td>
<td>Overseas</td>
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<tr>
<td>Supervisor(s):</td>
<td>Dr Daniel Mitchell, Dr Harpal Randeva</td>
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| Funding body (please tick as appropriate): | Chancellors International Scholarship ☐  
WMS Scholarship ☐  
WCPRS ☐  
Self-Funded X  
Via Health Ministry of Saudi Arabia |
| Has the funding been awarded?: | No – funding contingent on candidate receiving conditional offer from WMS |
| If the project requires consumables, please specify the amount and who is responsible for covering the cost: | £20,000 of consumables required per year to be provided by the Funding Body |

**Project Summary including key research questions, aims and anticipated outcomes (max 300 words)**

Regulation of haemostasis in humans is vital for cardiovascular health. The uptake and removal of coagulation factors & platelets from the bloodstream is an essential feature of circulatory homeostasis, and defects in this process could increase risk of coagulopathy. Haematological conditions such as disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia purpura (TTP) and haemolytic-uraemic syndrome (HUS) are associated with either the accumulation or depletion of platelets and coagulation factors in the circulation and can be life-threatening. Similarly, acquired coagulopathies in conditions such as diabetes and metabolic syndromes can increase atherosclerosis and risk of heart attack & stroke.

Recent findings highlight the importance of protein-carbohydrate interactions in the healthy clearance of coagulation factors and senescent platelets from the bloodstream by the liver (Grewal et al. Nature Medicine (2008) 14:648; Rydz et al. Blood (2013) 121:5228). In particular, two hepatic membrane C-type lectins have been identified as important carbohydrate recognition molecules – DC-SIGNR (CLEC4M; CD299) and the asialoglycoprotein receptor (ASGPR; Ashwell Receptor). Targets identified for these receptors include von Willebrand Factor (vWF) and desialylated platelets. However,
further circulating ligands - plus the precise oligosaccharides involved in receptor engagement – have yet to be described.

The full-time PhD project will focus on identifying ligands for DC-SIGNR and ASGPR from human platelet-enriched plasma and characterising the precise nature of the protein-carbohydrate interactions involved. This will utilise unique lectin resources & expertise within the Mitchell Group (Mitchell et al. Chem Sci (2017) 8:6974; Feinberg et al. Science (2001) 294:2163). Through direct links with Haematology and Endocrinology Departments at the University Hospital Coventry & Warwickshire (via Clinical Director Dr Harpal Randeva and the Arden Tissue Bank), we will investigate how these interactions influence – and are influenced by – important clinical conditions (e.g. hyperglycaemia). The work will involve state-of-the-art biophysical techniques (described below).

Key aims of the project will be:

1) characterising novel glycoproteomics within human haemostasis
2) investigating the influence of carbohydrates in coagulation and how this can assist patient evaluation & management.

Anticipated outcomes of the project would be the following:

1) Greater biochemical description of complex carbohydrates present within the human coagulation system
2) Understanding and visualising the range and mechanisms for lectin recognition of coagulation factors
3) Evaluation of the influence of metabolic and disease states in lectin-coagulation factor interactions.

**Describe the methodology and techniques to be employed (max 200 words)**

Liquid chromatography (housed at the CSRL) will be used to purify native and recombinant proteins, including oligomeric protein complexes, and also separate & characterise plasma and membrane glycoproteins, via ion exchange, size exclusion, and affinity chromatography methods.

Biolayer Interferometry (housed in the Department of Chemistry - Prof Gibson laboratory) will be used to characterise glycoprotein interactions and measure protein-glycoprotein binding kinetics. Electron microscopy (School of Life Sciences and University of Leicester - Prof Wallis laboratory) will be used to visualise lectin-glycoprotein complexes.

Glycoproteomics analysis via mass spectrometry will be available in collaboration with the Complex Carbohydrate Research Centre, University of Georgia in Athens, USA.