A mass spectrometry and chemical biology approach to dissecting the molecular basis of Tissue Factor regulation via post-translational modifications of RNA-binding proteins

Tissue Factor (TF, coagulation factor III) is a cellular activator of coagulation that is constitutively expressed by many parenchymal cells and is necessary for haemostasis. However, TF expression is selectively induced during inflammation in monocytes/macrophages and can drive thrombosis and lead to heart attacks and strokes. Our recent work has demonstrated that this response largely driven by post-transcriptional regulation of TF mRNA stability and translation which is mediated by ribonucleoprotein (RNP) complexes and their post-translational modifications (PTMs), including phosphorylation and ADP-ribosylation (Iqbal et al., Blood, 2014: 124). This proposal aims to combine chemical biology tools with mass spectrometry (MS) to elucidate how these PTMs function as regulatory switch to control the dynamics of RNP complex composition and ultimately drive TF expression during inflammation. Specifically, we will create novel NAD analogues, the co-factor for ADP-ribosylation, which will offer selective enrichment pathways for ADP-ribosylated peptides that are compatible with mass spectrometry (MS) for high-throughput site identification. This core technology will be combined with our recently developed MS proteomics pull-down workflows (including phosphoproteomics) using RNA probes to provide a holistic and dynamic description of the RNP complexes and PTMs that regulate TF mRNA stability. This could lead to the identification of novel therapeutic targets for preventing thrombosis.

**Supervisors:** Dr Peter DiMaggio | Prof Dorian Haskard | Prof Ed Tate

**Entry Requirements**

Applicants must hold, or expect to obtain, *a first class or upper second class degree in the physical sciences*, or will have obtained more than 50% of their course credits from physical sciences modules, from a recognised academic institution.

These studentships are restricted to UK students.

- UK students are defined as having the *settled status* in the UK (no restrictions on how long they can stay), and having been *ordinarily resident* in the UK for 3 years prior to the start of the studentship, as well as, for non EU nationals, not been residing in the UK wholly or mainly for the purpose of full-time education.
• Exception: we do have a small studentship proportion for EU nationals that have not been *ordinarily residing* in the UK for 3 years prior to the start of the studentship, however these are extremely competitive and once filled, you may be turned down based on your fee status (EU fee status)

Non-UK and non-EU students are welcome to apply if they are able to self-fund the 4 year programme.

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**Please clearly indicate in the Supporting Document section and Personal Statement, which studentship (or several) you are applying to.**