

**GTA Studentship for September 2024 entry**

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| **Scheme:** | **School of Chemistry Graduate Teaching Assistant (2024 Entry)** |

‘Payload-Releasing Electrophiles’ – a new disease-selective delivery strategy for diagnostics and therapeutics

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| **First Supervisor** | Dr Richard J. Hopkinson |
| **School/Department/Institute** | Chemistry |
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| **Additional Supervisor(s) or Collaborators**  | Dr. Kayoko Tanaka, Molecular and Cell Biology |

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| **Project Title** | ‘Payload-Releasing Electrophiles’ – a new disease-selective delivery strategy for diagnostics and therapeutics |
| **Project Highlights:** | 1. | Design and synthesise putative payload-releasing electrophiles (PREs) for targeting disease-relevant protein cysteine residues. |
| 2. | Test the reactions of the PREs with cysteine-containing peptides and proteins to determine their reaction efficiencies and selectivities. |
| 3. | Use the PREs to deliver fluorophores and cytotoxic drugs to human cells. |

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| **Project Summary**  |
| Diseased cells such as cancer cells often contain many surface-exposed cysteine residues on proteins due to mutations, over-expression and/or protein mis-folding. Targeting these nucleophilic cysteinyl thiols with electrophiles is well-established and has been used to alter the functions of cysteine-containing proteins and to treat disease. We intend to build on this approach by developing electrophilic chemicals that can additionally release a ‘payload’ after their reaction with cysteines (payload-releasing electrophiles, PREs). These PREs will enable the specific delivery of imaging agents or drugs to diseased cells. This new PRE cell targeting concept would not only induce therapeutically relevant modifications on the target proteins, but would also allow the efficiency of modification to be monitored in real time (e.g. by releasing fluorophores). This would be very useful for diagnostic applications and for drug validation studies. If the payload were a drug molecule, the method would also enable co-operative treatments that would (i) improve overall efficacy, (ii) would avoid the emergence of drug resistance (a common issue with cysteine-modifying drugs), and (iii) would reduce toxicity to healthy cells. This latter point is particularly important for cancer therapy, as the off-target toxicity of many anti-cancer agents precludes their clinical use. By incorporating electron-withdrawing groups on the PRE, we should also be able to induce reversible modification of the target protein, which in turn would enable catalytic generation of the payload. This would overcome any dosing issues associated with protein-induced payload release. We therefore propose that PREs have unprecedented potential to improve therapies for cancer and other diseases. The project will involve chemical synthesis (including structure design), recombinant protein expression and purification, NMR- MS- and fluorescence-based enzyme inhibition assays, and human tissue culture. Therefore, this highly multidisciplinary project will give an excellent grounding in biochemical and biomedically relevant techniques, and will ultimately produce a highly skilled multidisciplinary scientist. Training will be provided for all experimental methods. |

**Project / Funding Enquiries to:** Dr Richard J. Hopkinson richard.hopkinson@leicester.ac.uk

**Application enquiries to** **chempgr@le.ac.uk**

**See web page for application advice and link to the online application**