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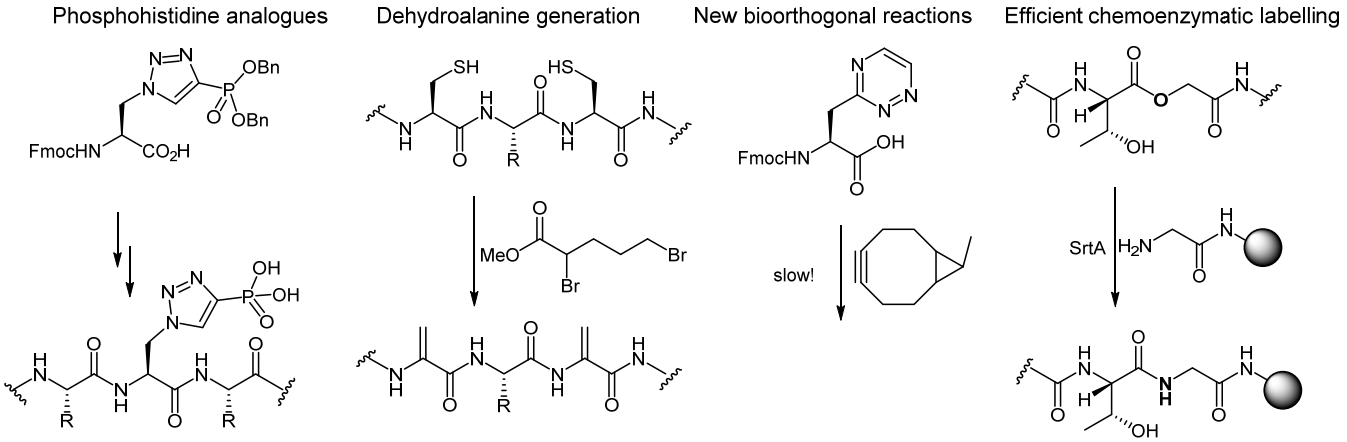
This proposal is representative of the projects currently on offer in our group. For more details of active research projects, please visit the Research and Publications sections of our webpage at: http://www.chem.leeds.ac.uk/MEW

A related project applying sortases to protein modification is available through the BBSRC DTP: https://www.findaphd.com/search/ProjectDetails.aspx?PJID=5841&LID=735

Chemical, Chemoenzymatic and Genetic Approaches to Protein Modification

Protein modifications underpin both the functions of proteins in the cell, and our exploitation of proteins as biotechnological and medical tools. Post-translational modification of proteins inside the cell is an essential for a wide variety of processes including signalling between cells, sensing of nutritional status and targeting particular proteins for synthesis and degradation at the appropriate time and place. For modern society, modification of proteins with dyes, affinity tags and other reagents such as PEG chains is essential for applications such as cellular imaging, immunological assay and drug-delivery. Over the last few years, we have developed a range of chemical and chemoenzymatic approaches to these challenges including the synthesis of stable analogues of phosphohistidine[1] which we hope to use to understand bacterial signalling, new methods for N-terminal modification of proteins[2] which we are currently using in studies of cellular endocytic trafficking as well as a variety of chemistries for protein post-translational modification[3].



A range of projects in this area are available, for example, you could build on our strategies for N-terminal modification of proteins to widen the scope of this reaction; you could use our chemical strategies for phosphohistidine analogue generation to generate peptides, and perhaps proteins, containing these modifications; or you could combine these approaches with the technology of Amber suppression to generate hyper-modified proteins for application in either biophysical or cellular assay.

Depending upon the precise area of the project, research work will require a broad range of skills to be used including: *protein expression and purification*; *organic synthesis* – to synthesise reagents for chemoenzymatic modification, precursors for phosphopeptide synthesis or peptides for assay; *assay development* – optimising protein modification approaches; *molecular biology* and *bacterial strain engineering* – to adapt our methods and combine them with approaches such as Amber suppression; and, ultimately, *biophysical* and *cellular characterisation* of modified proteins using fluorescence microscopy, SAXS or other techniques. The work may be carried out in collaboration with a number of national and international collaborators including Professor Arwen Pearson (Hamburg), Professor Andy Wilson, Dr Bruce Turnbull (Leeds) and Dr Stuart Warriner (Leeds).

References

[1] (a) T. E McAllister, K. A. Horner & M. E. Webb *ChemBioChem* (2014) **15** 1088-1091; (b) T.E. McAllister & M. E Webb. *Org. Biomol. Chem*. (2012) **10** 4043-4049; (c) T. E McAllister, M. G D. Nix & M. E Webb *Chem. Commun.* (2011) **47** 1297-1299;

[2] (a) D. J. Williamson, M. E. Webb & W. B. Turnbull *Nat. Protoc*. (2014) **9** 253-262; (b) D. J. Williamson, M. A. Fascione, M. E Webb & W. B. Turnbull *Angew. Chem. Int. Ed*. (2012) **51** 9377-9380;

[3] (a) P. M. Morrison, P. J. Foley, S. L. Warriner & M. E. Webb *Chem. Commun.* (2015) **51** 13470-3; (b) K. A. Horner, N. M. Valette & M.E. Webb *Chem.—Eur. J*. (2015) **21** 14376-81