Dr Megan Wright

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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 our webpage at: http://www.chem.leeds.ac.uk/People/Wright.html

Unravelling the interkingdom signalling of hormones by chemical proteomics

In this project you will synthesise and apply chemical tools to understand the mode of action of cell-cell signalling molecules.

Rising antimicrobial resistance is a global threat to human health and we need new approaches to tackle bacterial infections. There are ten times as many bacterial as human cells in the human body, yet our understanding of this complex microbiome is rather poor. Cells communicate via chemical signals and there is increasing evidence that bacterial and human cells 'listen in' on each other's communications. For example, bacteria respond to human signalling molecules such as hormones, peptides, lipids and steroids.[1,2] However, the mechanisms by which bacteria detect host signals are not clear: we lack information on how signals are sensed at the molecular level and how signal transduction pathways operate. In this project you will construct novel chemical tools and platforms to study such 'interkingdom' signalling.

In the group we are developing chemical tools to study small molecule-protein interactions in a wide variety of biological systems. We are interested in mapping ligand binding sites on receptors, profiling protein post-translational modifications,[3] and identifying the protein targets of bioactive compounds. One of our approaches is to synthesise functional probes that are 'weaponised' with reactive tags to covalently label proteins, and that are also equipped with additional tags to capture probe-protein complexes for further analysis (see Figure).[4] This capture chemistry is very versatile and can be used to attach different chemical groups for imaging or identification of proteins by mass spectrometry. In this project you will synthesise new functional probes and apply them to unravel the mode of action of human signals in bacterial pathogens.

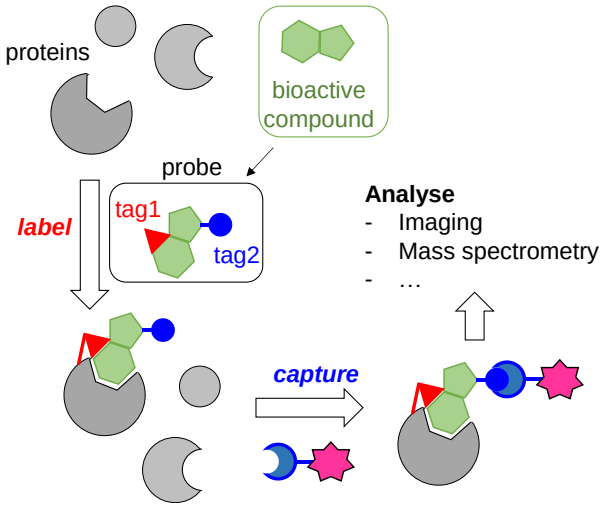

Figure. Concept of probe-based tagging of proteins and capture for analysis.

Over the course of the project you will receive training in organic synthesis, cell biology, biochemical techniques and mass spectrometry-based proteomics. This project would ideally suit a candidate with a synthetic organic chemistry background and a strong interest in applying chemistry to biological problems.

Please contact Dr Megan Wright (m.h.wright@leeds.ac.uk) for further details about this and other opportunities in the group.

References

1. Karavolos MH, Winzer K, Williams P, Khan CMA, *'Pathogen espionage: multiple bacterial adrenergic sensors eavesdrop on host communication systems'*, *Mol. Microbiol.*, **2013**, *87*, 455–465.
2. Kendall MM, Sperandio V, *'What a Dinner Party! Mechanisms and Functions of Interkingdom Signaling in Host-Pathogen Associations'*, *MBio*, **2016**, *7*, e01748-15.
3. Wright MH *et al., 'Validation of N-myristoyltransferase as an antimalarial drug target using an integrated chemical biology approach', Nat. Chem.,* **2014**, *6*, 112-121.
4. Wright MH, Sieber SA, *'Chemical proteomics approaches for identifying the cellular targets of natural products', Nat. Prod. Rep.,* **2016**, *33*, 681-708.