Department of Chemistry: Part III Project 2017/18

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Building dually-modified ADCs through regioselective chemistry

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We would like to welcome one Part III student into the group in October. Please email me to book a brief appointment to discuss projects and your interests. Our research group is working at the Whiffen, 106, 216 and 290 laboratories. Feel free to contact any of the researchers in the group (for this project, in particular Dr Maria Matos) for more information about our work.

Research

Our research group works at the interface of Chemistry and Biology, with a special focus on protein chemistry and targeted cancer therapeutics.[1,2]

Project description

A prototypical class of biomolecules in which the ability to introduce synthetic molecules in a site-selective manner is critical is antibody-drug conjugates (ADCs). ADCs consist of a tumour-homing antibody covalently linked to a potent cytotoxic drug through a cleavable linker. Recent studies have highlighted that the combination of ADCs with other small, untargeted chemotherapeutics may overcome differential drug sensitivities within heterogeneous tumour cell populations. In this project, we propose to address the major challenges in ADC technology by using innovative site-selective chemistry on native sequences to achieve complete product homogeneity and to build ADCs featuring two complementary drugs installed in two different, specific sites. The key to achieve these goals is the use of new methods developed by the group for the chemo and regioselective modification of a single lysine and/or cysteine on proteins that is orthogonal to other bioconjugation strategies (e.g., mixed-disulfide or thioether formation and oxime ligation). We will apply this method to build homogenous, dually modified ADCs bearing two drugs with complementary modes of action. Importantly, our approach can be readily applied to antibodies already used in the clinic and with proved targeting capability. The new ADCs will be characterized using advanced mass spectrometry and biophysical techniques.

The work plan includes the synthesis, purification and characterization of new linkers, study of reaction conditions and reactivity (lysine, cysteine and peptides models) and study in different proteins and antibodies used in drug delivery and imaging.

The project will provide the candidate training in organic synthesis and biological techniques related to protein modification (NMR, LC-MS, MS-MS, SDS-page, Flow-cytometry, circular dichroism, etc).

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[1] Boutureira, O.; Bernardes, G.J.L. *Chem. Rev.* **2015**, *115*, 2174-2195.

[2] Krall, N.; da Cruz, F.P.; Boutureira, O.; Bernardes, G.J.L. *Nature Chem* **2016**, *8*, 103-113.