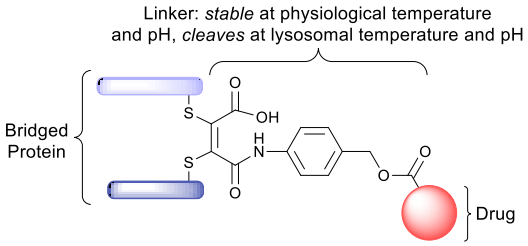
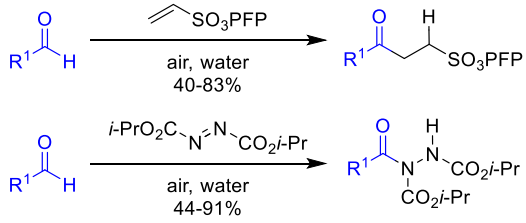
Research Summary

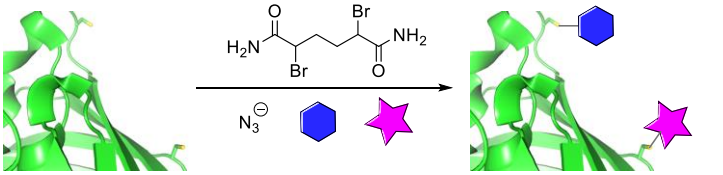
Reversible and Irreversible Chemoselective Bioconjugation - I have been involved in developing ground-breaking new methodologies, with the Baker and Caddick research groups, that allow for reversible and irreversible homogeneous protein modification.[1-8] For example, dihalomaleimides and dihalopyridazinediones can be used for the reversible, or irreversible, conjugation of biomolecules in high yield on various proteins.[1,2,4,7,8] Reversible constructs have been shown to disassemble in the reducing-environment of the cytoplasm of mammalian cells.[2] The methodology is currently being exploited in a variety of applications such as the homogeneous modification of antibodies and antibody fragments (see above),[8] and in reversible-affinity labelling for pull-down experiments.



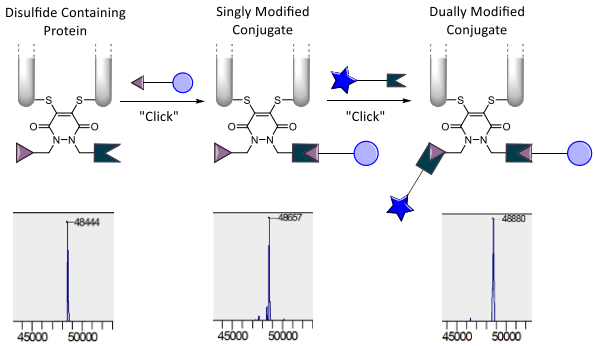
Aerobic Hydroacylation - In recent years, I have been involved in the development of a fundamentally novel approach to radical C-H bond activation that has been published in high impact journals such as *Nature Chemistry*.[9,10] This work is based on the discovery that acyl radicals generated from aldehydes in the presence of air can undergo hydroacylation with certain alkenes (see right). To date, the hydroacylation of vinyl sulfonates, vinyl sulfones, unsaturated esters and vinyl phosphonates has been reported, to generate a variety of unsymmetrical ketones.[10] I have also explored the aerobic hydroacylation of azo-dicarboxylates with various aldehydes to generate hydrazide dicarboxylates in high yields, even when employing aldehyde as the limiting reagent.[11] The use of stoichiometric amounts of aldehyde in hydroacylation processes offers the opportunity to employ high value aldehydes, which has been a major limitation of previous protocols.



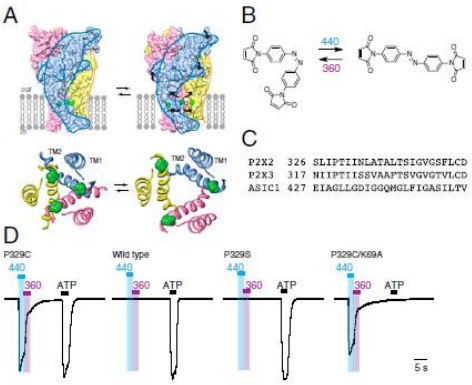
Site-selective Dual Modification of Proteins - I made a major contribution to the establishment of a new technology that allows for the site-selective dual labelling of proteins guided by local protein microenviroment (see left).[12] This is a fundamentally novel approach to achieve chemoselectivity on proteins that exploits the differential solvent accessibility of certain hydrogen atoms to selectivity promote or halt reaction. The methodology can introduce orthogonal handles which can be functionalised in a sequential manner, allowing for facile introduction of various cargos selectivity, *e.g.* drugs, radio labels or fluorophores.[12]



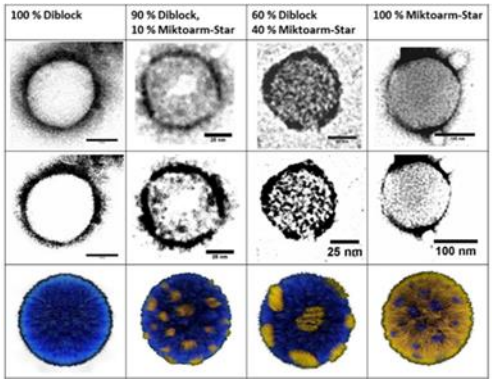
A plug and play approach to antibody-based therapeutics via a chemoselective dual click strategy - Although recent methods for the engineering of antibody-drug conjugates (ADCs) have gone some way to addressing the challenging issues of ADC construction, significant hurdles still remain. There is clear demand for the construction of novel ADC platforms that offer greater stability, homogeneity and flexibility. I, in collaboration with the Baker, Caddick, Pedley and Chester research groups, have made a significant step towards the ideal platform for next generation antibody-based therapeutics by providing constructs that combine site-specific modification, exceptional versatility and high stability, with retention of antibody binding and structure post-modification is delivered (see right).[13] The relevance of the work in a biological context in a cytotoxicity assay and a cell internalisation study with HER2-positive and negative breast cancer cell lines has also been demonstrated.



Optogenetic Approach to Light Controlled Ion Channel Opening - This project, in collaboration with Dr Liam Browne at Harvard University, is focused on bridging a thiol-reactive, light-sensitive azobenzene molecule across cysteines (introduced by mutagenesis) into ion channels.[14] Such chemically modified channels can then be opened by irradiation at 440 nm and closed by light at 360 nm, in the absence of any extracellular ligand, by a pushing and pulling force created by switching between the *cis*- and *trans*-states of the azobenzene. This has been exemplified to a great degree of success on various P2X receptors and an acid-sensing ion channel (see left). This overall work will extend our understanding of the molecular mechanism of gating and provides a tool to investigate the role of various receptors in intact cells and tissues. Moreover, a collaboration with Prof. Trevor Smart at UCL to appraise the methodology on the highly significant GABA-A receptor has recently been established. The appropriate cysteine mutations have been identified and the technology will be applied on this important receptor in the near future.



Versatile Constructs for the Construction of Polymersomes - The ability of nature to engineer functional and dynamic structures with tuneable size has been mimicked by synthetic amphiphiles for various applications. Of particular note are new advances in controlled polymerisation techniques that have allowed the design of a new class of polymer-based vesicles, polymersomes, which are based on the self-assembly of block-copolymers. In comparison to their lipid counterparts, polymersomes are significantly more stable in terms of mechanical and chemical properties and can also be functionalised in various ways. It is of great interest to design polymersomes for drug-delivery, and an important feature to ensure effective cellular entry is the polymersome's surface topology. In analogy with natural viruses (the most effective systems in entering cells), the ideal surface topology has to display clusters of ligands dispersed within cell inert materials. With Prof. Giuseppe Battaglia at UCL, I will be developing constructs that will allow for the creation of a variety of polymersomes, with our recent work already showing great promise for the construction of patchy polymersomes (see above). Such a control of ligand-receptor interaction will enable us to match closely the cell membrane topology and thus create more favourable energy landscapes for deforming the membrane.



ThioLogics - Thiologics is a UCL Business-owned company spun-out of the Department of Chemistry, UCL, in June 2011. The company aims to commercialise new bioconjugation technologies developed through collaboration between the Chudasama, Baker and Caddick research groups. ThioLogics is particularly focused on delivering technology that will enable the construction of homogeneous antibody drug conjugate therapeutics (ADCs) (www.thiologics.com).

References: *1) WO/**2013**/132268. 2) ChemBioChem, **2012**, 13, 39. 3) Chem. Commun., **2011**, 47, 8781. 4) WO/**2011**/018612. 5) Bioconjugate Chem., **2014**, 25, 611. 6) Chem. Commun., **2013**, 49, 8187. 7) Chem. Commun., **2015**, 51, 5279. 8) Org. Biomol. Chem., **2014**, 12, 7261. 9) Nature Chem., **2010**, 2, 592. 10) Chem. Commun., **2010**, 46, 133; Chem. Commun., **2014**, 50, 743; Org. Biomol. Chem., **2009**, 7, 235; Org. Biomol. Chem., **2013**, 11, 7301; Tetrahedron Lett., **2011**, 52, 1067. 11) Chem. Commun., **2011**, 47, 3269. 12) Chem. Commun., **2014**, 50, 4898; Chem. Sci., **2013**, 4, 3455. 13) Nature Commun., **2015**, DOI: 10.1038/ncomms7645; 14) Proc. Natl. Acad. Sci. USA, **2014**, 111, 521.*