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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/andrew-wilson/wilson-group.html

Designer Cross-Linking Chemistry To Probe Protein-Protein Interactions

The goal of this project is to develop a suite of cross-linking reagents with tunable reactivity across a range of timescales that allow high-yielding cross-linking and further analyses e.g. tracking in, or isolation from cells. In tandem with biochemical methods, this will allow us to move from analysis of static systems to dynamic systems and map structures of transient protein-protein interactions.

A major challenge in life-sciences research is to understand biomolecular processes with molecular and temporal resolution – this would allow identification of the transient intermediates that play key roles in signalling, folding, aggregation and mechanical motion (e.g. translocation) events. However, a molecular picture of such moving targets has proven elusive using conventional characterization techniques. Covalent cross-linking in tandem with biochemical methods can be used to provide structural information about non-covalent contacts in protein complexes, but current methods are deficient. The goal of this project is to develop a suite of covalent cross-linking reagents that possess (1) tunable reactive groups for high-yielding cross-linking over a variety of timescales (2) handles (fluorophores, affinity groups) for analyses in complex media e.g. cells. This will allow us to perform structural studies on dynamic processes involved in disease. The approach and tools we develop will (a) introduce general methods for widespread use throughout the cross-linking community and (b) provide new insight into the structures of transient interactions present during protein-protein interactions involving in aggregation and mechanical motion.

The student will perform a systematic evaluative study on the suitability of different cross-linking methods to the study of a range of proteins under study in the Radford group. This will be achieved through the synthesis of a range of bifunctional cross-linkers (having 2 reactive sites) bearing different cross-linking groups (NHS ester, diazirine, nitrene, PICUP groups) and orthogonal conjugation handles for isolation (e.g. biotin) or fluorescence tracking (e.g. BODIPY). Cross-links will be analysed by biochemical methods including mass spectrometry

This project is eligible for funding under the BBSRC Doctoral Training Programme to start in October 2017 (see: http://www.astbury.leeds.ac.uk/join/BBSRC/intro.php) – applications close on 5th January 2017. Please contact Prof. Andy Wilson (A.J.Wilson@leeds.ac.uk) for further details about this opportunity.

References

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