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

**Development of Modulators of Transient Protein-Protein Interactions**

This project will employ different approaches to design, synthesize, and characterize inhibitors of a transient protein-protein interaction involved in the development of amyloid fibril assembly – a process common to many degenerative diseases.

The development of small molecule modulators of protein-protein interactions (PPIs) facilitates pharmaceuticals development but also furthers our understanding of biological processes as a consequence of the ability to titrate such “probes” against a protein target in cellulo and in a temporal manner. “Transient” PPIs are more challenging in that they are a “moving” target, however such interactions correspond to those most likely to tip a biological process along an aberrant pathway. The Radford laboratory recently used state of the art NMR techniques to characterize both a stabilizing and a destabilizing PPI that leads to inhibition or promotion of amyloid formation by β2M; a protein with a central role in kidney related amyloidosis. This represents a powerful starting point for design of inhibitors. The project will integrate state of the art approaches developed in the Wilson group with biophysical and structural methods to provide a multidisciplinary training for the student that addresses fundamental challenges in drug discovery and our understanding of protein aggregation. The student will design and synthesize a series of candidates to inhibit the amyloid promoting interaction of the ΔN6 mutant of β2M with human β2M. Three strategies will be employed (a) design and synthesis of constrained peptidomimetics; (b) secondary structure mimetics of the key loop region observed in the ΔN6/ hβ2M interaction; and (c) the use of tethering (a covalent fragment approach reliant on disulfide formation) to identify fragments that bind a Cys mutant of ΔN6. The various approaches will be assessed for their ability to inhibit amyloid formation using kinetic assays and for the mechanism of their action using a battery of biophysical assays including NMR.

This project is eligible for funding under the BBSRC Doctoral Training Programme to start in October 2016 (see: http://www.astbury.leeds.ac.uk/join/BBSRC/intro.php) – applications close on 6th January 2016. Please contact Prof. Andy Wilson (A.J.Wilson@leeds.ac.uk) for further details about this opportunity.

**References**