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Inhibitors of Protein-Protein Interactions Involved in Cancer Development and Progression

The purpose of this project is to develop RULE-BASED APPROACHES for the design and synthesis of inhibitors of key protein-protein interactions (PPIs) involved in the development and progression of cancer.

The Bcl-2 family of protein-protein interactions play a central role in in the regulation of apoptosis and have therefore become the focus of anticancer drug development efforts.¹ Although the exact mechanism by which these proteins co-ordinate to determine cell fate remains under study, proteins within this family include the anti-apoptotic members (Bcl-2, Bcl-x_L and Mcl-1), pro-apoptotic members (BAK, BAX) and effector proteins (BID, BIM, PUMA and NOXA-B). The anti-apoptotic proteins contain a hydrophobic groove into which an α -helical BH3 domain of effector or pro-apoptotic proteins can bind (see e.g. Fig. 1a). As α -helix mediated PPIs,¹ the Bcl-2 family also represent a perfect testing ground for new stapling methodologies and helix mimetic scaffolds developed by our group (Fig. 1b-c).²⁻⁴ The student will

develop both approaches further to identify chemical probes that target selectively Bcl-2, Mcl-1, BAK and BAX. Key technical challenges will focus upon the development of inhibitors that can be used for ligand directed labelling of the target proteins, so that they can be "tracked" in cells and used to identify additional regulatory proteins of the Bcl-2 family through chemical proteomics approaches.

This multidisciplinary project will provide opportunities for the student to receive training in synthetic chemistry, protein expression and purification and structural molecular biology. There will be additional opportunities to exploit active collaborations with the Astbury Centre for Structural Molecular Biology.

Please contact Prof Andy Wilson (A.J.Wilson@leeds.ac.uk) for further details about this opportunity.

References

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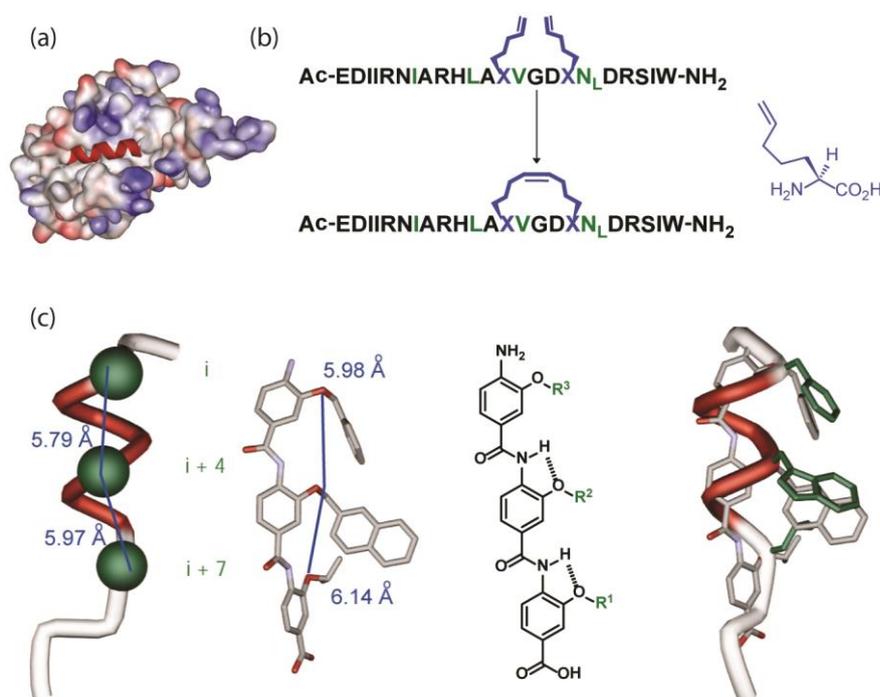


Figure 1. helix mediated PPIs as targets (a) Bcl-x_L/BAK interaction (b) peptide stapling developed in the Wilson group the covalent constrain biases the peptide towards a helical conformation improving potency and stability (c) helix mimetic developed in the Wilson group (a helix, a model mimetic, a chemdraw of the mimetic and overlay are shown)