Perturbation of α-Helix Mediated Protein-Protein Interactions

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Protein-protein interactions (PPIs) are of vital importance in many metabolic processes and hence being able to target them is of therapeutic interest.[1,2] The large, mostly flat, contact interfaces between proteins were considered to be challenging to target effectively with small drug-like molecules however, in recent years, some small molecule candidates have progressed into clinical trials.[3] These developments were made possible by the identification and targeting of a small sub-set of residues on the protein surface that contribute most of the free energy of binding known as 'hot spots'.[4]

A common motif found at the interface of PPIs is the α-helix. This provides a regular structure that can serve as a template for small molecule and peptide development. Amongst others, the PPIs of several oncoproteins are α-helix mediated, such as p53/*h*DM2 and NOXA-B/MCL-1.[5] We aim to develop generic approaches to the discovery of effective α-helix mediated PPI inhibitors using a combination of *in silico* design, synthetic methodology and experimental validation.

Our approaches to the development of small molecule inhibitors have been twofold: computationally informed rational design to dissect key determinants of protein-protein binding interactions, and the synthesis and screening of small molecule libraries to identify selective small molecule inhibitors. Using a predictive approach, coupled with synthesis, and subsequent determination of the binding affinities of a library of variant peptides, we have developed 'hot-spot' models for several α-helix mediated PPIs. We have then utilised these models to progress towards discovery of selective small molecule inhibitors. This has deepened our understanding of PPI topography, increased the robustness of our approach and will facilitate the identification of low molecular weight PPI inhibitors.

References:

1 M. M. R. Arkin and J. A. Wells, *Nat. Rev. Drug Discov.*, 2004, 3, 301–317.

2 A. J. Wilson, *Chem. Soc. Rev.*, 2009, **38**, 3289–3300.

3 M. R. Arkin, Y. Tang and J. A. Wells, *Chem. Biol.*, 2014, 21, 1102–1114.

4 T. Clackson and J. A. Wells, *Science.*, 1995, **267**, 383–386.

5 V. Azzarito, K. Long, N. S. Murphy and A. J. Wilson, *Nat. Chem.*, 2013, 5, 161–173.