Targeting protein-protein interfaces using small molecules holds great potential for elucidating complex cellular pathways, for target validation in drug discovery and ultimately developing the next generation of molecular therapeutics. Many functional protein-protein interactions are dictated by the post-translational modification (PTM) of specific amino acids of one or both of the partner protein, thereby expanding Nature’s inventory of recognition patterns and regulatory control mechanisms. In my talk I will illustrate two structure-based studies of targeting protein interfaces that selectively read PTMs of amino acids on partner proteins. Firstly, I will describe the discovery of novel drug-like small molecules that target the interface between the von Hippel Lindau protein (pVHL), which functions as part of a multi-subunit E3 Ubiquitin Ligase complex, and the alpha subunit of the Hypoxia Inducible Factor (HIF-a). This protein-protein interaction, which is driven by hydroxylation of a proline residue in HIF-a, is responsible for targeted polyubiquitination and proteasome-dependent degradation of HIF-a, a crucial regulatory mechanism in oxygen sensing. Disruption of this interaction in cells is expected to mimic the hypoxic response and is a potential target for the treatment of chronic anemia and acute ischemia. Secondly, I will discuss progress towards fragment-based design of chemical probes of bromodomains, a family of epigenetic readers of lysine acetylation in histones and other proteins. These studies aim to provide new tools to interrogate druggability and probe selectivity within the bromodomain family, to elucidate the biological role of individual bromodomains within the human proteome, and ultimately to validate them as drug targets against disease.

CBC SEMINAR ANNOUNCEMENT

Dr Alessio Ciulli
University of Cambridge

Structure and fragment based design of small molecule chemical probes of protein interfaces that read posttranslational modifications

Date: 27th September 2011 (Tuesday)
Time: 11am – 12:30pm
Venue: NTU SPMS CBC Building Level 2, Conference Room
Host: Assoc. Professor Chen Hongyu