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Antibodies as research tools to find new chemical matter

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Protein-protein interactions (PPIs) are of critical importance in most of biological cellular processes including DNA repair, immune, and allergic responses. Despite their therapeutic relevance, PPIs are intrinsically challenging targets due to complexity of interactions, assay tractability and the lack of well-defined binding pockets at the interacting surfaces. In the quest for small molecule drug candidates targeting PPIs, there have been many different approaches adopted, which include: use of existing lead or drugs, natural products, high-throughput screening and more recently established powerful fragment-based drug discovery. At UCB we have integrated the fragment-based methodology with biological and structural information obtained from antibody-validated protein targets, to develop specific small molecule inhibitors of PPIs. An ensemble of biophysical methods (i.e. SPR, ITC, FRET, MS and ligand-based NMR), corroborated by functional data, were employed to identify and validate fragment hits that constituted the starting point for our PPI inhibitor drug discovery programs. We have also employed antibodies as research tools to hold target proteins in biologically active conformations, aiding the discovery of new small molecules for challenging targets. By holding the target protein in biologically relevant conformations, new sites (in particular allosteric sites), which would otherwise be inaccessible, may become available for binding. The ability to capture the target protein in a specific conformation with high affinity for a significantly long time opens the possibility for a small-fragment molecule screening.

Biography

Marta Westwood has obtained his PhD in Nano-materials from Cranfield University in 2007. In 2011, he has joined Structural Biology group led by Alaistair Lawson at UCB. For the past five years, he has been developing expertise in small molecule drug discovery using a fragment based approach. He has also been involved in the assay development for a novel antibody-enable drug discovery approach. Prior to joining UCB, he was awarded a Post-Doctoral Fellowship at the Institute of Food Research in Norwich to study the mono and multilayer films used to encapsulate active ingredients for a controlled and site-specific delivery within the GIT. During his time at IFR he has worked on numerous projects including a commercial project for Pfizer focused on AFM imaging of proteins and polysaccharides constituting vaccines.

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