EuroSciCon

3rd Edition of International Conference on

Advanced Spectroscopy, Crystallography and Applications in Modern Chemistry

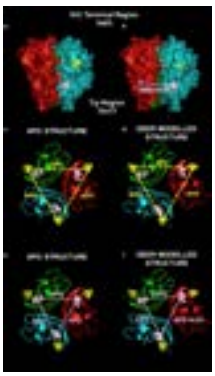
June 04-05, 2018
London, UK

Alastair Lawson, Struct Chem Crystallogr Commun 2018, Volume 4
DOI: 10.21767/2470-9905-C1-005

ANTIBODY-ENABLED SMALL MOLECULE DRUG DISCOVERY

Alastair Lawson
UCB, Slough, UK

Targeting protein-protein interactions with small molecules presents a number of well documented challenges, including the largely flat, featureless interfaces for many published structures. While structural information has undoubtedly assisted in drug discovery through suggesting direction and properties for compound elaboration, the guidance provided can only be truly valuable if the structure on which it is based is an accurate representation of the precise conformation of the protein being targeted. Crystal structures, although visually compelling, may not represent the biologically relevant conformation of the target, and can suffer from distortion due, for example, to intermolecular contacts in the lattice. Orthogonal biophysical techniques, such as Double Electron-electron Resonance (DEER), in conjunction with spin labeling at specified points on the surface of target proteins, can be used to probe natural conformational sampling, and provide distance measurements, which can be compared to those obtained from equivalent positions in crystal structures. Existing crystal structures may thus be adjusted, using advanced molecular dynamics simulations, to accommodate the distance measurements from DEER and create working models of target proteins in biologically relevant conformations. For example the image below shows how a crystal structure of apo TNF was adjusted using distance data from DEER, to generate a working model of a new conformation of the target, which may be helpful in drug discovery.



Recent Publications

1. Importance of Rigidity in Designing Small Molecule Drugs to tackle Protein-protein Interactions through stabilization of Desired Conformers. Lawson ADG; MacCoss M; Heer J. Journal of Medicinal Chemistry Doi 10.1021/acs.jmedchem.7b01120, 2017
2. Natural Conformational Sampling of Human TNFalpha Visualized by Double Electron-Electron Resonance. Carrington B; Myers WK; Horanyi P; Calmiano M; Lawson ADG. Biophysical Journal. 113(2):371-380, 2017
3. Combining Molecular Scaffolds from FDA Approved Drugs: Application to Drug Discovery. Taylor RD; MacCoss M; Lawson AD. Journal of Medicinal Chemistry. 60(5):1638-1647, 2017
4. Computational design of an epitope-specific Keap1 binding antibody using hotspot residues grafting and CDR loop swapping. Liu X; Taylor RD; Griffin L; Coker SF; Adams R; Ceska T; Shi J; Lawson AD; Baker T. Scientific Reports. 7:41306, 2017.
5. Small Molecule Targeting of Protein-Protein Interactions through Allosteric Modulation of Dynamics. Cossins BP; Lawson AD. Molecules. 20(9):16435-45, 2015
6. Rings in drugs. Taylor RD. MacCoss M. Lawson AD. Journal of Medicinal Chemistry. 57(14):5845-59, 2014
7. Antibody-enabled small-molecule drug discovery. Lawson AD. Nature Reviews Drug Discovery. 11(7):519-25, 2012.

Biography

Alastair has been closely involved with the discovery of UCB/Celltech's therapeutic antibodies, including Mylotarg®, Besponsa®, Cimzia®, romosozumab, dapirolizumab pegol, olokizumab, bimekizumab and UCB7665. Alastair led the development of UCB's proprietary antibody variable region discovery platform, and is now applying structure-based, rational design to antibody discovery. He pioneered UCB's small molecule protein/protein interaction initiative, in which information derived from antibodies is applied to the discovery and design of new chemical entities. Current research interests include the use of function-modifying antibody fragments to define specific conformations of target proteins, linking X-ray crystallography, orthogonal biophysical techniques, molecular dynamics simulations and antibody technology to small molecule fragment screening

alastair.lawson@ucb.com