IN BRIEF

VIRTUAL SCREENING

Binding mode prediction of cytochrome P450 and thymidine kinase protein–ligand complexes by consideration of water and rescoring in automated docking

de Graff, C. *et al. J. Med. Chem.* 17 Feb 2005 (doi:10.1021/jm049650u)

Despite the fact that water molecules can have an essential role in ligand–protein binding, most computational 'docking' methods for virtual ligand screening ignore water-mediated interactions between proteins and ligands. This study presents the first comprehensive evaluation of the effects of explicit active-site water molecules on molecular-docking-based binding-mode prediction with three widely used docking programs. Consideration of water molecules, and pooling and rescoring of all solutions generated by the docking programs, significantly improved the quality of prediction of the binding modes.

CARDIOVASCULAR DISEASE

Circulating transcriptome reveals markers of atherosclerosis

Patino, W. D. *et al. Proc. Natl Acad. Sci. USA* **102**, 3423–3428 (2005)

Circulating monocytes, which mediate inflammation in atherosclerosis, might serve as accessible reporters of disease. Patino *et al.* compared the *in vivo* transcriptomes of monocytes from patients with atherosclerosis and normal patients, and provide data that the *FOS* gene is a marker and mediator of atherosclerosis. Similar approaches examining the circulating transcriptome in other conditions might also be valuable.

STROKE

Recombinant activated factor VII for acute intracerebral hemorrhage

Mayer, S. A. *et al. N. Engl. J. Med.* **352**, 777–785 (2005)

Early intervention with haemostatic therapy might improve outcomes after intracerebral haemorrhage — the least treatable form of stroke. In this trial involving ~400 patients, treatment with recombinant activated factor VII within 4 hours of the onset of intracerebral haemorrhage was shown to limit the growth of the haematoma, reduce mortality and improve functional outcomes at 90 days.

KINASES

Chemical genomic profiling to identify intracellular targets of a multiplex kinase inhibitor

Kung, C. *et al. Proc. Natl Acad. Sci. USA* **102**, 3587–3592 (2005)

Identifying which kinases are targeted by protein kinase inhibitors is a key challenge in validating their use as therapeutic agents or chemical tools to probe biology. The authors describe a strategy to address this challenge that uses a direct comparison between microarray transcriptional signatures elicited by an inhibitor of unknown specificity and those elicited by highly specific pharmacological inhibition of engineered kinases, which they use to identify the targets of a cyclin-dependent kinase inhibitor of previously unknown specificity.

G-PROTEIN-COUPLED RECEPTORS

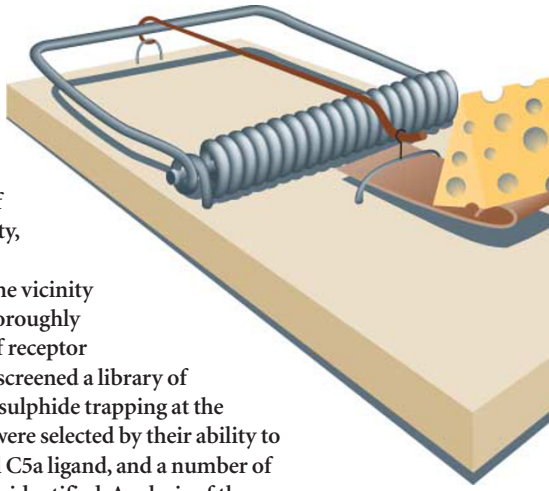
Setting traps for drug discovery

In a recent issue of the *Proceedings of the National Academy of Sciences*, researchers describe a technique for 'trapping' small molecular fragments at the proposed binding site of a G-protein-coupled receptor (GPCR). This could reveal how the receptor is activated and also facilitate the development of small-molecule drugs that target it.

GPCRs comprise the largest single class of cell-surface receptors. They transmit signals from the outside to the inside of the cell and are involved in many important physiological processes, including the detection of light, smell, sound and taste. GPCRs are also implicated in many diseases, and almost two-thirds of currently marketed drugs are thought to interact with these transmembrane receptors. But despite their importance in biology and medicine, our understanding of how ligands bind and activate GPCRs is still relatively limited.

Now, however, Jim Wells and colleagues have used an ingenious disulphide trapping technique to characterize ligand binding and activation of the chemokine C5a receptor (C5aR), and suggest that the approach might be suitable for analysing other GPCRs.

The main requirement for disulphide trapping is that the ligands have an exchangeable thiol group (–SH), which can form reversible disulphide bonds with cysteine (Cys) residues engineered into the receptor in the vicinity of the ligand-binding/activation site. Ligands that bind the receptor are therefore brought into close proximity to the engineered Cys residues and become 'trapped' at the ligand-binding site through disulphide-bond formation, enabling their functional effects to be assessed.



Previous work has shown that thiol-containing peptides are able to bind Cys residues engineered into the transmembrane region of C5aR and modulate its activity, indicating that the receptor's binding/activation site is in the vicinity of these residues. To more thoroughly analyse the structural basis of receptor activation, the current study screened a library of 10,000 small molecules for disulphide trapping at the same Cys sites. Compounds were selected by their ability to inhibit binding of the natural C5a ligand, and a number of agonists and antagonists were identified. Analysis of these compounds showed that small changes in the structure of the trapped molecule could either greatly reduce binding, or switch a compound from being an agonist to an antagonist. Furthermore, a key amino-acid residue was identified in the receptor's binding site that has a crucial role in determining whether a ligand behaves as an agonist or an antagonist. So, structural changes to either the ligand or its receptor can modulate agonism or antagonism.

The researchers suggest that this technique could be used to trap small-molecule mimics of natural ligands for drug discovery.

Clare Ellis

References and links

ORIGINAL RESEARCH PAPER Buck, E. & Wells, J. A. Disulfide trapping to localize small-molecule agonists and antagonists for a G-protein-coupled receptor. *Proc. Natl Acad. Sci. USA* **102**, 2719–2724 (2005)
FURTHER READING Buck, E., Bourne, A. & Wells, J. A. Site-specific disulfide capture of agonist and antagonist peptides on the C5a receptor. *J. Biol. Chem.* **280**, 4009–4012 (2005)