Poster I-18

Identification of Druggabable "Hot Spots" in Ligand Binding Pockets by Computational Solvent Mapping of Proteins.

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Short Abstract: Here we describe the application of the CS-Map algorithm to the identification of druggable subsites within a ligand binding pocket. The accuracy of CS-Map results is illustrated on a set of fifty proteins for which high affinity drug-like compounds have been developed and structural information is available.

Long Abstract:
Druggability is defined as the capability of a protein to bind lead-like compounds with high affinity. This property has been described previously in NMR-based screening studies that reported a high correlation between the hit-rate and the druggability of a specific binding pocket on a protein1. Here we describe the application of a computational method for binding site prediction, the CS-Map algorithm2, to the identification of druggable subsites, or "hot spots", within a ligand binding pocket. Unlike other existing computational methods for binding site identification, the CS-Map algorithm is capable of resolving the affinities and binding modalities of lead-like fragments on a residue-level within the binding pocket. This is accomplished via a multi-step method that involves (1) placement of a lead-like chemical fragment on the surface of the protein in both predicted and unknown binding locations (2) a search for low energy binding conformations (3) a refined free energy evaluation of the conformations resulting from the search and (4) interaction-based clustering of fragments bound with low free energies. Mapping of multiple fragments on an individual basis results in the creation of consensus sites, e.g. hot spots, established by the aggregation of low energy clusters of multiple fragment types at specific locations on the protein. Further analysis of the consensus sites allows for the characterization of contacts that particular residues in the binding pocket make with chemical fragments. Hydrogen bonding and hydrophobicity patterns can also be extracted from the data, resulting in a pharmacophore depiction of the binding region.

The accuracy of the CS-Map algorithm in the prediction of druggable hot spots is illustrated by the analysis of a set of fifty proteins for which both high affinity drug-like compounds have been developed and structural information is available through the Protein Data Bank (http://www.pdb.org). Hot spots resulting from the mapping data for these proteins are consistent with the interactions that the known drugs make with each protein. Of particular interest is Renin aspartic protease, an important therapeutic target for the treatment of hypertension. While several peptide-like Renin inhibitors have been developed3, currently only one therapeutic agent, Aliskiren4, has entered Phase III clinical trials. Mapping results for Renin are consistent with the binding conformation of Aliskiren versus peptidomimetics,

highlighting the importance of particular residue contacts in the peptide binding pocket to the development of high affinity, lead-like compounds for Renin inhibition. Based on these results, we conclude that the information provided by CS-Map can contribute substantially to in silico fragment-based drug discovery efforts.

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