



Computational Methods for Assessing Existing and Proposed Pharmaceuticals

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ABSTRACT:

We have recently developed a computational method to determine the geometric potential [1] which describes the ligand binding sites of 3-dimensional protein structures. Subsequently we developed a fast approach to search for these sites in a high throughput mode [2] across the druggable proteome. The goal of the project is to use these tools to search for competitive binding of major pharmaceuticals which might explain observed side effects, reposition an existing drug, or ultimately point the way towards further lead optimization. So far we have been able to offer an explanation for the side effects observed using select estrogen receptor modulators (SERMS), for example tamoxifen [3] and potentially reposition an existing drug for use in the treatment of drug resistant TB. Work with other drugs as well as some evolutionary implications of shared binding sites will be reported.

[1] L. Xie and P.E. Bourne 2007 A Robust and Efficient Algorithm for the Shape Description of Protein Structures and Its Application in Predicting Ligand Binding Sites BMC Bioinformatics, 8(Suppl 4):S9

[2] L. Xie and P.E. Bourne 2007 Detecting Evolutionary Linkages Across Fold and Functional Space with Sequence Order Independent Profile-profile Alignments. PNAS, Submitted

[3] L. Xie, J. Wang and P.E. Bourne 2007 In Silico Elucidation of the Molecular Mechanism Defining the Adverse Effect of Selective Estrogen Receptor Modulators. PLoS Comp. Biol., 3(11) e217