Universität Basel

Research Project

Drug Discovery at Protein-Protein Interfaces: Simulation and Quantification of Small-Molecule Binding to Unstructured Binding Sites

Third-party funded project

Project title Drug Discovery at Protein-Protein Interfaces: Simulation and Quantification of Small-Molecule Binding to Unstructured Binding Sites
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Project start 01.10.2008
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Status Completed

Aim: Development of a novel scoring function, allowing for dynamics, solvation and entropic effects associated with small-molecule binding to unstructured regions located at the protein surface. Subsequently, a mixed-model approach — i.e. simulating the binding at the three-dimensional structure of the target protein followed by quantifying the binding strength using multi-dimensional QSAR (mQSAR) — shall be used to simulate the binding of small ligands to various proteins, in particular lectins. Emerging drug candidates emerging shall be verified through chemical synthesis, followed by biological assaying.

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Relevance: Targeting the interfaces between proteins has huge therapeutic potential, but discovering small-molecule drugs that disrupt protein-protein interactions is an enormous challenge. A prerequisite to identify suited candidate molecules *in silico* is the ability to identify and quantify their binding mode. While, in principle, the biophysical laws employed in current computational concepts should also suffice to model surface phenomena, several factors have up to date jeopardized a sweeping success of an otherwise sound approach. Apart from the inherent difficulty to identify the binding mode at unstructured binding sites, the quantification of solvation effects and entropic contributions associated with ligand binding represent the major obstacle.

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Targets: Unlike the peripheral nervous system, the injured adult mammalian central nervous system inherently lacks the capacity for axon regeneration. Although neurite outgrowth is basically possible,it is actively blocked by inhibitor proteins such as the myelin-associated glycoprotein. Selectins play a key role in the inflammatory process, that is, the recruitment of leukocytes from blood vessels into inflamed tissue. Because excessive infiltration of leukocytes can induce acute or chronic reactions, the control of leukocyte extravasation is of great pharmaceutical interest. All physiological ligands of the selectins contain the tetrasaccharide epitope sialyl Lewis^X, the lead structure in selectin antagonist research.

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Means: In the past decade, our laboratory has developed a series of *in silico* tools (force-field development, automated flexible docking, mQSAR, toxicity prediction). Both our flexible docking concept and the mQSAR software *Quasar* and *Raptor* would seem to be suited for the tackling of small-molecule

binding to unstructured, extended binding sites located at the surface of proteins. The underlying force field includes directional terms for hydrogen bonds, salt bridges and metal–ligand interactions allowing for an appropriate treatment of those key interactions.

Keywords protein-protein interactions, small-molecule binding to unstructured binding sites lo- cated at protein surfaces, multi-dimensional QSAR, computer-aided drug discovery, lectin antagonists
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Add publication

Published results

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