[L10] PDB-scale Identification of Druggable Cavities at and Nearby Protein-Protein Interfaces

Didier Rognan

Laboratoire d'Innovation Thérapeutique, UMR 7200 CNRS-Université de Strasbourg, 67400 Illkirch, France

Until recently, mostly single macromolecules (proteins, nucleic acids) have been considered as potential drug targets. Out of the 71,500 proteins currently annotated in the human proteome, only about 300 targets [1] have been addressed by current drugs, and the large majority of single targets are still awaiting first-in class drugs. Beside single targets, large-scale genomics and proteomics [2] have identified complex networks of targets and pathways regulating physiopathological processes in a coordinated manner. The current human protein-protein interactome has been estimated at between 130,000 [3] and 650,000 [4] complexes, out of which only a tiny amount is known, and only a very few has been the object of a drug discovery initiative. Protein-protein interactions (PPI) therefore describe a new biological space that attracts more and more attention, with already 36 PPI inhibitors [5] under clinical development, notably in oncology.

We herewith present a computational flowchart aimed at fostering drug discovery from the structural knowledge of protein-protein interfaces. The flowchart is made of several steps utilizing in-house knowledge-based algorithms and machine learning models [6-9] to answer key issues in detecting reliable PPIs, identify druggable cavities at the interface or its close vicinity, and then screen compound libraries for hits able to fit a cavity-based pharmacophore. After presenting the workflow, two applications focusing on ligands biased towards G protein-coupled-receptor homodimers will be reported.

Bibliography:

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