Accurate human structural proteome-wide characterization of protein-drug interactions

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Current FDA-approved drugs remain underutilized due to an incomplete understanding of drug-protein targeting and their mechanism of action. These drugs were shown to interact not only with the intended therapeutic target(s) but also with many other protein targets (off-targets). This polypharmacology can be both beneficial (drugs can be repurposed, effective combination therapies can be designed) and harmful (the off-target interactions can lead to side-effects). Conventional off-targets identification methods rely on counterscreens against a selected set of enzymes and receptors, which is costly, time-intensive and could be biased. Compared to the experimental screens, computational methods are more cost and time effective, allow for screening of a much larger number of targets, and provide insights into the molecular mechanisms of protein-drug interactions (PDIs). These *in-silico* methods were found to be successful in the context of drug repurposing and identification of the off-targets. However, the existing computational approaches are characterized by a relatively low predictive performance and are limited to the elucidation of interactions with proteins that were already characterized to bind drugs. The latter means that they cannot be used to infer interactions with the remaining proteins and when a given protein interacts with two chemically dissimilar compounds.

We will discuss our contributions in the area of proteome-wide characterization of PDIs. We will introduce our state-of-the-art inverse ligand predictor, ILbind [*Structure* 2012, 20:1815-1822], which was empirically shown to accurately predict drug targets across protein fold space, even for proteins that have vastly different structure than the proteins that are known to interact with a given drug. We recently developed a computational platform that extracts and characterizes both putative and native/known PDIs in human genome (proteome) using ILbind and relevant resources including Ensembl, DrugBank, BindingDB, PDB, UniProt, and Ingenuity. We will present our preliminary results focused in the development of protein–protein–drug–side-effect/disease association network, which combines our putative and known protein–drug interactions, protein–protein interactions, and protein–side-effect/disease associations, for a few dozens of the FDA-approved drugs. We will wrap up the talk focusing on a case study that analyzes top-scoring putative targets for a popular immunosuppressant cyclosporine A.