Hiding In Plain Sight: Distilling Protein-Ligand Hotspots from Hundreds of Hsp90 Crystal Structures

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Protein flexibility is important for ligand binding but often ignored in drug design. Considering proteins as ensembles rather than static snapshots creates opportunities to target dynamic proteins that lack FDA-approved drugs, such as the human chaperone, heat shock protein 90 (Hsp90). Hsp90α accommodates ligands with a dynamic lid domain, yet no comprehensive analysis showing how the lid conformation is impacted by ligand properties is available. To date, some 300 ligand-bound Hsp90α crystal structures are deposited in the Protein Data Bank, which enables us to consider ligand binding as a perturbation of the protein conformational landscape. By estimating binding site volumes, we show that Hsp90α crystal structures are best described by 3 distinct major and 4 minor lid conformations. Supported by retrospective docking, each conformation creates unique hotspots that bind chemically distinguishable ligands. Clustering conformation-ligand pairs revealed insightful exceptions to these trends driven by crystal packing. Overall, this study creates a drug discoverer's roadmap for "hitting a moving target" that motivates an ensemble-based view of drug design and cautions against overinterpreting individual crystal structures (Stachowski & Fischer, J. Med. Chem., 2022, 65, 13692-13704).