The dynamics of molecular design

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Controlling biochemical pathways through chemically designed modulators may provide novel opportunities to develop therapeutics and chemical tools. Herein, we tackle this problem through computational studies of the Hsp90 chaperone machinery and several representatives of client kinases.

First, we will examine the origins of the stimulation of ATPase and closure kinetics in Hsp90 by designed allosteric modulators. To this end, we apply atomistic molecular dynamics (MD) simulations and analysis of the effects of the ligand-protein cross-talk on the internal dynamics of the chaperone. A critical aspect of this study is the development of a quantitative model that correlates Hsp90 activation to the presence of a certain compound. In particular, the model makes use of information on the dynamic adaptation of protein structure to the presence of the ligand, which allows to capture the most relevant conformational states in the activation process. We test this model by rationally designing and experimentally validating new allosteric modulators with improved stimulation profiles and encouraging anticancer activities.
This computational protocol is then applied to the Hsp90 mitochondrial homolog Trap1, revealing new allosteric ligands with high isoform selectivity.

Next, we focus on Hsp90 clients: starting from the analysis of the TK family of proteins, we develop a model that quantitatively correlates the energetic stabilization profile of each kinase to its “Hsp90-clientness”. We then extend this model to other kinase families, identifying the determinants of folding/unfolding that correlate with the tendency to form complexes with Hsp90. We use this information to design kinase-mimics that target Hsp90 and may act as Hsp90-targeted Protein-Protein inhibitors