Application of a novel structural analysis tool to identify potential combinatorial drug therapy candidates against invasive candidiasis

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Invasive candidiasis results in 30-50% mortality rate in immuno-compromised patients [1]. Evolution of drug resistance in the eukaryotic fungal pathogen *Candida albicans* has led to the emergence of combinatorial drug therapy as a promising treatment strategy [2]. In this work we describe the role and mechanism of two natural triterpenes (gedunin and celastrol) as potential combinatorial drugs with the current *de facto* anti-fungal drugs such as azoles and echinocandins. The interaction between the chaperon HSP90 and its co-chaperon sba1 plays a pivotal role in basal tolerance of *C. albicans* against azoles and echinocandins. Gedunin and celastrol inhibit this vital interaction. Through a combination of homology modeling, molecular docking and molecular dynamics (MD) studies, we shed light on this inhibition mechanism. Further, we confirm that the human homologue of the sba1 co-chaperon, p23 is not affected by the triterpenes. A novel structural alphabet based tool called *PBmapclust* [3] was used to correlate the structural changes occurring during MD to the interactions stabilizing the binding (Figure 1).

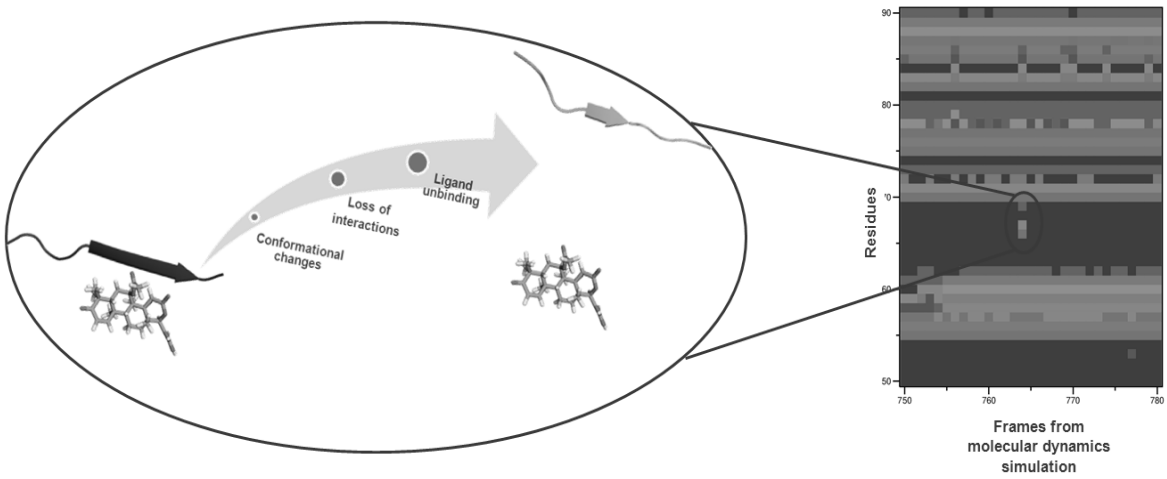

Figure 1: Correlating structural changes from MD to the interactions stabilizing the binding of ligand to protein using the *PBmapclust* tool.

Bibliography :

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