Abstract of Presentation

Note: This paper should be typed in "Times New Roman" of 12pt.

Presentation Title(Should be no more than 20 words):

"Structure based rational design of new inhibitors for cancer therapy"

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Abstract :

In the recent years, *in silico* methods have profoundly changed the drug discovery process by massively expanding the fraction of the chemical space sampled and by speeding up the process of lead discovery and optimization. Whereas virtual high-throughput screening methods have shown some promising results, fragment based approaches are becoming increasingly popular as they allow an even larger fraction of the chemical space to be sampled. Fragment based algorithms bring several methodological problems, like the need to have a consistent description of the energetics of the system from individual fragments, all the way to complete ligands bound to the active site. Over the last few years, we have developed EADock, a general purpose docking software especially suited for fragment based applications. EADock makes use of a universal energy function based on the CHARMM force field and the Generalized Born solvation energy. The conformational sampling relies on a multi-objective lamarkian genetic algorithm. EADock has been benchmarked on several standard protein ligand structural databases like the LPDB, showing a consistent success rate of around 80%. Recent optimizations of the approach will be presented.

Using EADock and a fragment based approach, we have developed small molecule inhibitors for several key target in oncology. The results obtained for the indole-amine 2,3-dioxygenase (IDO) will be presented in detail. For this project, around 100 new molecules have been synthetized based on the in silico results and tested in an enzymatic inhibition assay; 50% of them were shown to be active, with the best Ki around 100 nM.