S29-5 *in silico* approaches in fragment-based drug discovery

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Molecular modeling and simulations can contribute to two stages in the process of fragment-based drug discovery. Firstly, these technologies expected to decrease the costs and durations of fragment screening by pre-selection of fragments supplied for X-ray crystallography, NMR or SPR. Secondly, they can enhance the efficiency of SBDD (Structure-based drug design) for achieving lead compounds starting from hit fragments. We will present our computational approaches for each stage. We developed a new category of docking scoring function which takes into account the weak interactions like halogen-pi interaction and weak hydrogen bonds. We implemented this scoring function to in-house docking program, PD-dock, and applied it to a screening of Hsp90 binding fragments. We will also present approaches for enhancing lead generation. The strategies of lead design starting from hit fragments are categorized to fragment-linking, fragment-evolution or fragment-merging. Our program, "Fragment-linker", designs a linker connecting two fragments which bind to neighboring sites each other. We will present the results of evaluation of this method.