# Ligand-Sensing Cores - Large Scale Analysis and Application

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The structure-based design of small molecule modulators of protein function is a crucial step in medicinal chemistry. Different approaches deal with the exploitation of structural knowledge in combination with data of known ligands of the target of interest. The automated method developed in our group aims to find so-called 'ligand-sensing cores', i.e. a similar arrangement of secondary structure elements constituting the binding site that leads to the binding of similar scaffolds [1]. The presented results show two basic application domains of this approach: idea generation for drug design and the prediction of potential off-target effects.

First, the method was applied on Trypanothione Synthetase (TryS). This enzyme is crucial for the survival of different organisms of the species Trypanosoma and Leishmania - the causative agents of so-called neglected diseases like Chagas disease or african trypanosomiasis. Encouraged by the knowledge, that TryS and certain protein kinases share similar ATP-binding site ligands [2], the similarities between TryS and ATP-binding proteins were analysed using the 'ligand-sensing cores' approach. Based on the results, a virtual screening workflow was established to exploit this knowledge. MD simulation studies and molecular docking contributed to the selection of promising molecules and we now strive to provide a proof of concept using biochemical assays.

The second outcome presented here is the analysis of an all-against-all comparison of all Ligsite-defined [3] binding sites of all structures stored in the Protein Databank. Preliminary analysis showed a huge amount of similar ligand-sensing cores within proteins showing a low overall structural and sequence similarity. Using the established database of common 'ligand-sensing cores' throughout the PDB, it is now possible to analyze interesting targets within seconds. This approach is especially useful for the prediction of possible off-targets or the establishment of interesting polypharmacology.

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