

POSTER PRESENTATION

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More than a rigid framework: molecular design using secondary structure element information

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The structure-based design of small molecule modulators of protein-ligand binding and protein-protein interaction is a key component in drug discovery. The underlying protein interactions can be regarded based on structural similarity of the involved secondary structure elements [1].

The most prominent example is the protein fold of a protein domain that is more conserved than the amino acid sequence and proteins with similar fold but dissimilar sequence and function can bind similar ligands. Similar ligand binding can also occur between different proteins that have a similar spatial arrangement of secondary structure elements around the ligand binding site ("ligand-sensing cores") independent from the overall fold [2]. Analogous to this, similar protein-protein interfaces can occur within different protein folds showing different function, since the structural space of protein interfaces is degenerated and is represented by roughly 1000 distinct interfaces [3].

These similarities in otherwise unrelated proteins can be useful in the design of protein function modulators. The successful applications in molecular design described in literature using predicted polypharmacology in protein-ligand binding will be shown and the analogy in the design of protein-protein interaction inhibitors and the potential of polypharmacology prediction will be discussed.

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