A quantitative understanding of PPI stabilization by molecular glues – a crucial role for peptides

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Stabilization of protein-protein interactions (PPIs) with molecular glues is one of the most current and challenging topics in chemical biology and drug discovery. The three-body-problem (2 different proteins and a molecular glue) constitutes a conceptually completely fascinating and unique challenge both regarding its fundamental biophysical understanding and for the identification of novel molecular matter. Our group combines organic synthesis, protein chemistry, structural biology, and supramolecular chemistry to perform chemical biology studies on PPIs with the aim to enable innovative medicinal chemistry entries for 'molecular glues' for PPIs.

Intrinsically Disordered Proteins (IDPs) represent one of drug discovery's major challenges. Due to their high degree of conformational freedom, IDPs have no defined pockets for binding small molecules. Molecular glues that can strengthen protein-protein interactions (PPIs) are a revolutionary technology for drug discovery. The hub protein 14-3-3 regulates many IDPs and ID domains of multidomain proteins via phosphorylation-dependent PPIs. Stabilization of 14-3-3 PPIs with small molecular glues provides a unique entry point to render IDPs druggable and mitigate the aberrant behaviour of malfunctioning IDPs, for example in neurodegenerative diseases.

While inhibition of PPIs by small molecules has expanded the proteome suitable for therapeutic intervention, the opposite chemical-biology strategy of PPI stabilization by small molecular glues is, despite a recent surge of interest, remarkably underexplored. The lack of mechanistically understanding PPI stabilization impedes systematically identifying molecular glues and limits progress to drug IDPs.

Via a combination of mechanistic studies into 14-3-3 PPIs stabilization and the development of novel molecular concepts to drug the composite pockets of 14-3-3 PPIs, we aim to unlock the 14-3-3 interactome for novel drug discovery.
The general challenge centers around the three-body-problem (2 different proteins and a molecular glue). This unique element of PPI stabilization constitutes a conceptually fascinating and unique challenge both regarding its fundamental biophysical understanding and for the identification of novel molecular matter. Our group combines organic synthesis, protein chemistry, structural biology, and supramolecular chemistry to perform chemical biology studies on PPIs with the aim to enable innovative medicinal chemistry entries for 'molecular glues' for PPIs.

The presentation will highlight a combination of chemical biology and medicinal chemistry approaches to help to unravel the underlying complex interaction mechanisms. This conceptual approach to PPIs allows to recognize and apply supramolecular concepts such as multivalency and cooperativity within the context of drug discovery and as leading principles in for example compound optimization and selectivity towards specific PPI. Specific examples regarding the 14-3-3 PPI with the Estrogen Receptor, Tau and ChREBP will be highlighted to illustrate the functionality of 14-3-3 molecular glues on the cellular level and beyond.

References: