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My research focuses on small-molecule stabilization of protein-protein interactions (PPIs). Whereas inhibition of PPIs is meanwhile a well-established and successful area in Drug Discovery, targeted stabilization of PPIs is still underrepresented. This is surprising given the fact that a number of natural products like rapamycin, FK506, brefeldin, and forskolin mediate their physiological effects by stabilizing specific protein complexes. In addition, also a number of molecules originating from Drug Discovery like tafamidis and lenalidomide have been shown to work as PPI stabilizers. Thus it is indeed feasible to target regulatory protein complexes with small, PPI-stabilizing molecules to perturb biological systems for basic research or even achieve a therapeutic effect.

Work in my lab focus on 14-3-3 protein-protein interactions. The reason for this is two-fold: i) 14-3-3 proteins are wide-spread hub proteins that interact with several hundred other proteins in human physiology and are thus involved in almost every disease field. Consequently, we are following projects related to cancer, neurodegeneration (Alzheimer's and Parkinson's Disease), metabolic diseases, inflammation and cystic fibrosis. If we should succeed in developing specific stabilizers for 14-3-3 PPIs with e.g. p53, B-Raf, Tau, LRRK2, AS160, NFκB, and CFTR, we could make a significant impact in both Chemical Biology and Drug Discovery. ii) The concept of 14-3-3 PPI stabilization is "chemically validated" by the natural products fusicoccin and its derivatives, e.g. stabilizers of 14-3-3 interaction with Gab2 (cancer)1 or CFTR (cystic fibrosis) 2.

The goal to exploit a chemical biology principle like PPI stabilization for translational purposes can best be realized in close collaboration with medicinal chemists and the pharma industry. In this regard, our newly funded EU Horizon2020 project "Targeted Stabilization of Protein-Protein Interactions – TASPPI" is the ideal initiative to establish 14-3-3 PPI stabilizers as a novel approach in Drug Discovery. The TASPPI consortium comprises groups from 5 universities (Eindhoven, Dundee, Leeds, Lille, Prague, Siena), 3 pharma companies (AstraZeneca, GSK, UCB) and two SMEs (LDC, Taros Chemicals). In the next 4 years we hope to be able to show that 14-3-3 PPI stabilization is indeed a viable strategy not only for basic research but also in translational Chemical Biology.

References

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