Targeted modulation of protein–protein interactions (PPIs) with small, drug-like molecules is one of the most promising approaches in modern drug discovery (Arkin et al. 2014; Milroy et al. 2014). Not only the number of potentially addressable PPI targets with estimates between 130,000 and 650,000 (Venkatesan et al. 2008; Stumpf et al. 2008; Zhang et al. 2012) is significantly higher than those of single protein targets, but also a number of natural products and molecules from drug discovery initiatives illustrate that PPIs are addressable with small molecules. Both these facts mean that in principle every disease can be tackled by small-molecule PPI modulators, especially those that lack good, conventional targets like enzymes, GPCRs, ion channels, or nuclear receptors. In addition, for hard-to-target pathogenicities like Alzheimer's or metabolic diseases, PPI modulation may be a viable option definitely to be considered. However, despite these encouraging vantage points, identification and optimization of small-molecule modulators of PPIs still poses a formidable challenge.

1 Protein–Protein Interactions in Health and Disease

Direct physical interactions of proteins are essential to all processes in living organisms. One example is the reception and propagation of growth signals that can start with the binding of a proteinaceous signaling molecule like the epidermal growth factor to its cell-surface receptor. This ligand/receptor recognition event then triggers the assembly and activation of signaling complexes at the cytosolic site of the plasma membrane recruiting adapter proteins like Gbr2 and Sos as well as small G proteins like Ras. Ras then activates the Raf kinases, again mediated by direct physical interaction. In a subsequent phosphorylation cascade, Raf then stimulates other kinases (like MEK and ERK) that ultimately leads to gene activation via transcription factors (Wellbrock et al. 2004). As each of these steps necessitates direct binding of the proteins in this signal transduction chain, small molecules that bind to the involved interfaces of either one of these partners could disrupt this pro-proliferative signaling. Another principal possibility to attenuate such a pathway would be small-molecule stabilization of the binding of negative regulators to Raf (like RKIP, Zeng et al. 2008). The control of the spatial distribution of proteins is another important aspect of functional regulation performed by PPIs. For example, the pro-inflammatory transcription factor NFκB is prevented from nuclear import upon complexation with its negative regulator IκB (Shih et al. 2011). Stabilization of this protein complex could hence result in a therapeutic benefit in autoimmune diseases.

Direct regulation of biochemical activities of enzymes by PPIs is observed repeatedly. The phosphatase calcineurin, for example, is activated by binding to Ca^{2+}-activated calmodulin and repressed by cabin (*c*alcineurin-*b*inding prote*in*) or calcipressin (Liu 2009). Another important process involving PPIs is the functional constitution of transcriptional complexes. Although transcription factors of the Tcf/LEF family directly bind to DNA, transcription starts only when co-activators like β-catenin additionally interact with Tcf/LEF (Shitashige