# Targeting Protein-Protein Interactions to Treat Protein Misfolding Diseases

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To maintain protein homeostasis (proteostasis), each cell must carefully balance the decision to retain or degrade a protein. This decision is not always made correctly, as apparent in neurodegenerative diseases, where misfolded proteins accumulate in diseases neurons. Thus, there is interest in better understanding how cells maintain proteostasis, with the goal of finding ways that balance can be therapeutically restored. For each protein, the decision to "degrade" is typically driven by direct, physical protein-protein interactions (PPIs). For example, chaperone binding is used to discern whether the protein is unfolded. Likewise, PPIs between the protein, chaperones and the ubiquitin conjugation machinery are often used to drive turnover. Our goal is to understand and perturb these PPIs using a chemical biology strategy. Here, we focus on an interesting and relatively under explored category of PPIs: those that occur at N- and C-termini. The chemical environment at the ends of a polypeptide is often unique (e.g. pKa values, dynamics) and these regions can be a hotspot for post-translational modifications (PTMs). Thus, new strategies might be required to chemically manipulate terminal PPIs. Here, we will discuss progress on developing methods towards that goal, including high throughput methods for studying terminal PPIs.