Targeted Protein Stabilization with DUBTACs

Significance: Irregular protein degradation plays a critical role in the pathogenesis of many diseases, such as cystic fibrosis and several forms of cancer. Thus, targeted protein stabilization (TPS) offers a novel therapeutic strategy for such cases. Utilizing an approach analogous to proteolysis-targeting chimeras (PROTACs), Nomura and co-workers developed deubiquitinase-targeting chimeras (DUBTACs) as small-molecule recruiters of the deubiquitinase OTUB1 to stabilize polyubiquitinated proteins of interest tagged for proteasomal degradation.

Comment: Using chemoproteomics, Nomura and co-workers identified OTUB1 as an ideal candidate for recruitment and demonstrated acrylamide ENS23 be a selective ligand for OTUB1 with no loss of activity. DUBTAC NJH-2-057 was generated by linking ENS23 to the pharmaceutical drug lumacaftor to target mutant chloride channel ΔF508-CFTR, the degradation of which is associated with the cystic fibrosis phenotype. In vitro assays demonstrated a dose-dependent and time-responsive restoration of CFTR levels and function, justifying further investigations into DUBTAC-mediated TPS.