Haven't got a glue: design principles for molecular glue degraders

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Molecular glue degraders are an emerging therapeutic strategy that exploit induced protein-protein interactions to drive ubiquitin-mediated degradation of challenging targets. However, their discovery has largely relied on serendipity, constraining their broader potential. By systematically analyzing correlations between small-molecule cytotoxicity and E3 ligase expression across human cancer cell lines, we identified CR8—a cyclin-dependent kinase (CDK) inhibitor—as a molecular glue degrader that induces degradation of cyclin K by recruiting the DDB1-CUL4 E3 ligase to CDK12–cyclin K. Our structural, biophysical, and cellular investigations reveal that CR8 exploits a solvent-exposed pyridyl moiety to engage DDB1 at key interfacial residues, particularly Arg928, while bypassing the need for a canonical DCAF substrate receptor. Notably, we found that other, diverse chemical scaffolds can also drive this interaction, challenging the notion of steep structure-activity relationships commonly associated with molecular glues. Furthermore, small chemical modifications can precisely tune the balance between CDK12 inhibition and cyclin K degradation, with degradation occurring independently of strong kinase inhibition. These findings define a novel class of cyclin K-targeting agents and provide a foundation for the rational design of molecular glue degraders, opening new avenues for therapeutic innovation.