Molecular Glue Induced Targeted Protein Degradation

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Until recently the world of drug discovery was partitioned: the druggable and the undruggable proteome. The rules that defined this landscape were developed based on whether a protein had been previously liganded and its function blocked or attenuated as required. A new modality has subsequently entered the fray, and Targeted Protein Degradation radically rewrites classical rules of druggability through the understanding of Thalidomide (an IMiD), and its related analogs in modulating the endogenous ubiquitin proteosome system. The molecule serves as a glue to direct the binding of proteins to the ubiquitin ligase substrate receptor CRBN leading to ubiquitination and degradation. To exploit this mechanism for drug hunting, an expansive library of IMiDs and related CRBN binders were elaborated and screened using the Allo-GlueTM screening system developed at Orionis Biosciences which identifies novel neosubstrates that are "glued" and recruited to the small molecule CRBN binary complex. Structural biology plays a key role in the understanding of glue-induced recruitment and degradation. Here we will present some of our structural understandings of Cereblon-based molecular glues using both canonical and non-canonical recruitment. Structural biology plays a key role in the understanding of glue- induced recruitment and degradation. Here we will present some of our structural understandings of Cereblon-based molecular glues using both canonical and non-canonical recruitment.