

## Discovery and structural characterization of a VHL-mediated molecular glue degrader targeting cysteine dioxygenase

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VHL is one of the most widely exploited E3 ligases to induce ubiquitination and subsequent targeted protein degradation. Although many VHL-mediated bifunctional proteolysis-targeting chimeras (PROTACs) are known in the literature, bona fide example of small molecule glue degrader that recruit client protein to interact with VHL remains scant. Here, we report a small molecular glue degrader discovered from protein microarrays. Using several biochemical, biophysical and cellular assays, we demonstrate these compounds induce neo-interactions between VHL and cysteine dioxygenase (CDO1), leading to the polyubiquitination and degradation of CDO1. Structural characterization of this VHL/CDO1/glue ternary complex maps the degron to a composite surface formed by multiple discontinuous regions of hCDO1. Collectively, our studies reveal the mechanism of action of a novel small molecular glue degrader that directly recruits CDO1 to VHL, presenting a new avenue for targeted protein degradation.