Experimental and Molecular Therapeutics

Abstract 6411: Discovery of covalent ligands to novel E3 ligases enables bispecific degraders with highly differentiated protein degradation across a broad range of targets

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Abstract

Introduction: Targeted protein degradation is a novel therapeutic modality that holds great promise. Current bispecific degraders have been mostly built using reversible ligands against two well characterized E3 ligases, CRBN and VHL. Features unique to each particular E3 ligase, such as its tissue expression pattern or its intrinsic catalytic efficiency could ultimately impact the *in vivo* bioactivity of any bifunctional drug based on it. Therefore, discovering ligands to novel E3s has the potential to enable a new class of drugs with substantially differentiated pharmacology compared to CRBN- or VHL-based degraders. Our unique covalent small molecule library and proteomics platform is an ideal tool for discovering ligands against novel E3s.

Experimental plan: Utilize Vividion's chemical proteomics platform to screen for ligands capable of covalently engaging novel E3s and driving targeted degradation when configured in bifunctional formats.

Summary of Results: Initial screens identified covalent ligands capable of potently engaging numerous E3 ligases, including members of the Cullin E3s, other RING-containing ligases and HECT E3 ligases. We describe here a representative molecule from this screening effort that was advanced to engagement potencies of < 10 nM while maintaining a selectivity window of over a thousand-fold relative to the next closest target. Proof-of-concept studies were designed by incorporating this E3 ligand into bifunctional degraders using 3 different target recruiting ligands capable of binding to FKBP12, BRD4 or to multiple kinases. These bifunctional molecules demonstrated profound and sustained degradation of all tested targets *in vitro,* with near complete degradation observable within 4 hours and potency ranges of < 10 nM. These covalent degraders were consistently more potent compared to several published CRBN- and VHL-based degraders designed to target the same proteins. When tested *in vivo*, a representative molecule from this series was capable of achieving near complete degradation of the intended target across multiple tissues. These molecules consistently outperformed similarly configured CRBN- and VHL-based degraders when assessed head to head in mouse degradation studies, and several molecules demonstrated > 50% degradation the target proteins at doses < 1 mg/kg. The current data suggest covalent ligands to novel E3 engagers could prove useful for future degrader-based drug design against multiple cancer targets. Further, Vividion's chemical proteomic platform is well suited for discovering novel covalent E3 ligands capable of supporting targeted degradation applications in cancer.

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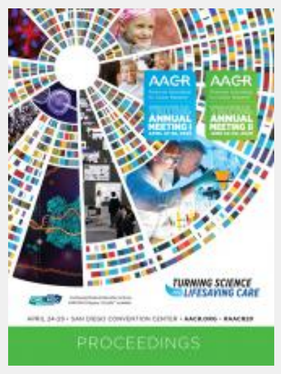

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