28P Discovery of Potent PROTAC Degraders of KRASG12C Based on a Reversible Non-covalent KRAS Binder

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Background

Targeted protein degradation (TPD) using proteolysis targeting chimeras (PROTACs) has arisen as a powerful therapeutic modality for eliminating disease-causing proteins from cells[1]. PROTACs employ heterobifunctional small molecules to chemically induce the proximity of target proteins with E3 ubiquitin ligases to ubiquitinate and degrade specific proteins via the proteasome. TPD is an attractive therapeutic strategy for expanding the druggable proteome[2]. This paper is to design and synthesize a series of novel PROTAC compounds targeting the KRAS G12C mutationwhich make up over 50% of all KRAS mutant LUAD (Lung Adenocarcinama) (13% of total LUAD tumors)[3].

Methods

In our study, targets mutant KRAS G12C has been designed and developed which is composed of reversible non-covalent KRAS binder linked to E3. We conducted the design, synthesis, and evaluation of PROTAC KRAS degraders using the VHL or cereblon ligands, and different classes of non-covalent KRAS binder. I We fully determined the optimal linker lengths and types needed in our PROTAC molecules for potent and effective KRAS degradation.

Conclusion

Our study first developed a series of new and potent reversible non-covalent KRAS-PROTAC molecules. This current study demonstrated that conformational restriction of the linker in PROTAC KRASG12C degraders, coupled with modifications of KRASG12 binder portion are critical in the finding of potent KRASG12C degraders.

Results

Through extensive optimization of the linker and modifications of the KRAS binder portion of the compounds, we have discovered a set of exceptionally potent KRAS degraders with moderate membrane permeability and good plasma stability. More than 50 compounds were designed and synthesized using various linkers, E3 ligands and KRASG12C binders. Among these, compounds containing a cyclopentane, a cycloheptane, a cyclooctane were all much less potent and effective in reducing KRASG12C than compounds containing a piperidine and an azapane group in linkers. Almost all compounds maintained good selectivity to KRASG12C, suggesting that the introduction of a substituent on the piperidine N-atom of our warhead was an effective strategy. The results also showed that PROTACs used thalidomide to recruit cereblon were unsuccessful in degrading endogenous KRAS G12C under 10 μM and over 24 h. Our degrader series based on a non-covalent inhibitor and a ligand that recruits VHL successfully engaged VHL in cells, bound KRASG12C in vitro, induced VHL/KRASG12C dimerization, and degraded KRASG12C in cells in a VHL-dependent manner. The representative compound induced KRASG12C ubiquitination and degradation with the DC_{50} value of 0.1 μM and Dmax value of 90%. Its discovered that the PROTAC degrader, the structure of the linker plays a key role in inducing degradation of the target protein.

References

[1] C.V. Dang, E.P. Reddy, K.M. Shokat, L. Soucek, Drugging the ‘undruggable’ cancer targets, Nat. Rev. Cancer . 2017,17

[2] P.P. Chamberlain, L.G. Hamann, Development of targeted protein degradation therapeutics, Nat. Chem. Biol. 2019,15

[3] Prior, I. A.; Lewis, P. D.; Mattos, C. A comprehensive survey of Ras mutations in cancer. Cancer Res. 2012, 72