Proteolysis Targeting Chimaeras Induce the Degradation of Epidermal Growth Factor Receptor in Lung Cancer

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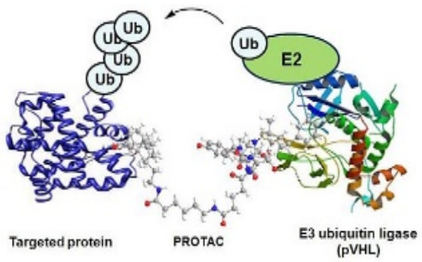
Objective

The goal of this research was to determine the effectiveness of specially designed EGFR PROTAC degraders, assess their specificity, and compare their efficacy to that of the current inhibitor, gefitinib.

Background

- Small molecule drugs like enzyme inhibitors are limited in efficacy because they are unable to target non-enzyme proteins and tend to lose therapeutic potential over time.
- Proteolysis targeting chimaera (PROTAC) shows promise in targeting proteins and disrupting signaling pathways. PROTACs induce the degradation of specific target proteins via the ubiquitin-proteasome degradation system by bringing E3 ligase and the target protein in close proximity. [1]



Kim (2010), OpenWetWare

- In cancer, especially with non-small cell lung cancer (NSCLC), overexpression of the epidermal growth factor receptor (EGFR) promotes cell proliferation, metastasis, angiogenesis and increased cell survival.[2]
- The PROTAC degraders synthesized and assessed in this project were designed as follows:

E3 Binder: CRBN/VHL

Linker

EGFR Binder: gefitinib (EGFR inhibitor)

Results

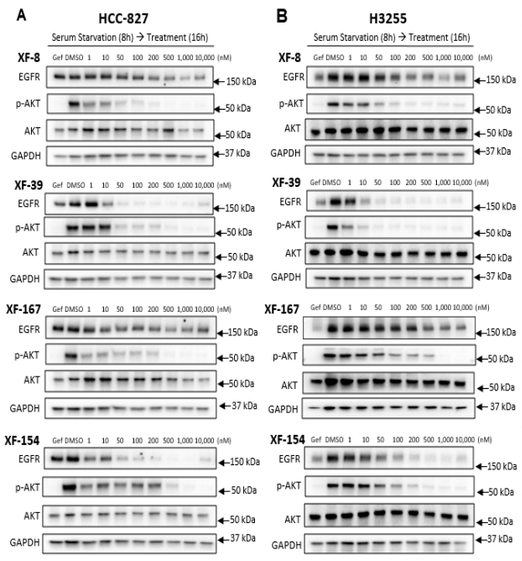


Figure 1. PROTACs mediate the degradation of EGFR and downregulate phosphorylation levels for downstream targets in a dose dependent manner.

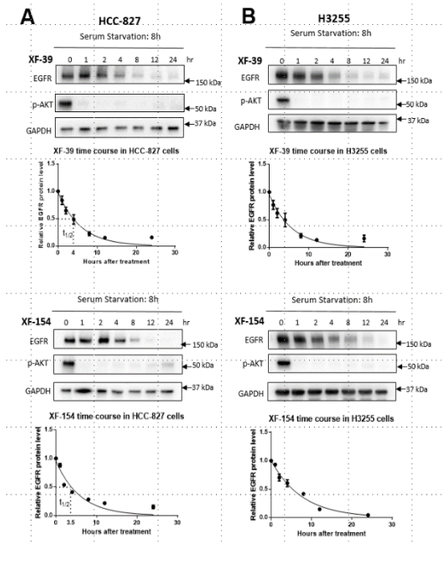


Figure 2. PROTACs facilitate the rapid degradation of EGFR.

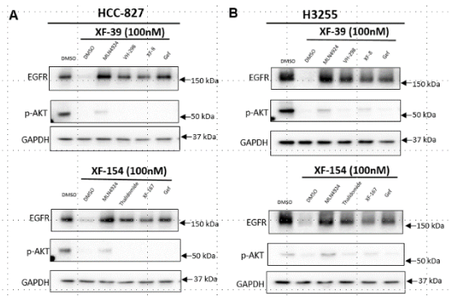


Figure 3. The degradation mechanism of PROTACs rely on E3 ligases and the ubiquitin proteasome system.

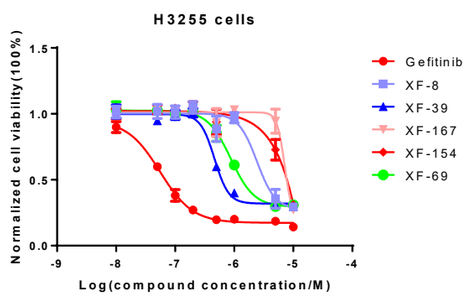


Figure 4. PROTACs inhibit the proliferation of NSCLC cells.

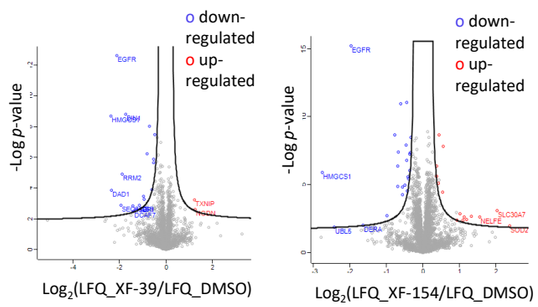


Figure 5. PROTACs exhibit high specificity for EGFR.

Methods

To characterize the EGFR PROTACs, we used:

- **HCC-827 and NCI H-3255** human lung carcinoma cell lines with mutant EGFR
- **Western Blot** to assess protein levels of EGFR and downstream targets upon drug treatments
- **Cell Proliferation Assay** to determine impact of PROTACs on lung cancer cell proliferation
- **Liquid Chromatography Mass Spectrometry** to assess the specificity of the EGFR PROTACs

Conclusion

- Gefitinib based EGFR PROTACs decrease the levels of the oncogenic mutant EGFR in a dose-, time-, and proteasome-dependent manner
- PROTACs downregulate targets of the EGFR pathway and inhibit cell proliferation, eliminating all oncogenic functions of a cancer-causing protein
- The high specificity of EGFR PROTACs could reduce toxicity of lung cancer treatment
- PROTAC is an effective strategy to target mutant EGFR, and perhaps other oncogenic proteins

Future Work

- Analyze the biochemical structure that contributes to the effectiveness of certain PROTACs over others, comparing previous and newly designed degraders

Acknowledgements and Bibliography

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2. da Cunha Santos G, Shepherd FA, Tsao MS. 2010. EGFR mutations and lung cancer. Annual Review of Pathology: Mechanisms of Disease. [accessed 2018 Sep 10].