BRD4 Degradation by PROTACs Represents a More Effective Therapeutic Strategy than BRD4 Inhibitors in Ovarian Cancer

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Abstract

- BRD4, a member of the bromodomain and extraterrestrial domain (BET) family of proteins, has emerged as an attractive oncology target.
- BET inhibitors have shown promising results in a number of preclinical settings, including ovarian cancer (OvCa).
- We have designed Proteolysis Targeting Chimeras (PROTACs) against BRD4, which are heterobifunctional small molecule degraders containing a BRD4 binding moiety and a ligand for the E3 ubiquitin ligase VHL.
- PROTAC treatment leads to rapid and efficient degradation of BRD4 across OvCa cell lines (0.1µM<EC<1nM).
- BRD4 PROTACs have more potent anti-proliferative activity than BET inhibitors in OvCa cell lines. However, this activity is highly variable (0.6nM<EC<1µM).
- We have performed RNA-sequencing on 5 OvCa cell lines to identify a genetic signature correlated with sensitivity to our BRD4 PROTACs.
- BCLxL, recently shown to predict BET inhibitor sensitivity in cancer, emerges as a potential clinical biomarker candidate in our analysis.
- Finally, BRD4 PROTACs are potent in vivo agents and efficacious in an A2780 tumor model of OvCa wherein BET inhibitors are inactive.

Summary

- We have developed PROTACs that are potent BRD4 degraders in ovarian cancer cell lines and in tumor xenografts.
- BRD4 PROTACs are efficacious degraders in vitro and in vivo, and result in stasis in an A2780 tumor model following intermittent IV dosing.
- Ovarian cancer lines show differential sensitivity to PROTAC mediated BRD4 degradation.
- We have found a number of genes known to be associated with chemoresistance and disease outcome in ovarian cancer to be differentially regulated in highly PROTAC sensitive cell lines.
- We hypothesize that BCLxL has the potential to be a clinical biomarker, with low levels being predictive of tumor sensitivity to BRD4 degradation in ovarian cancer.

PROTAC treatment is efficacious in an A2780 subcutaneous xenograft mouse model

BRD4 PROTACs are potent degraders in OvCa cell lines

PROTAC treatment results in pronounced apoptosis in sensitive OvCa cell lines

PROTACs are potent BRD4 degraders in vivo