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Poster # 375

BRD4 Degraders Produce Long-lasting Loss of BRD4 Protein and Robust Efficacy in Burkitt's Lymphoma, Multiple Myeloma, and Prostate Cancer Cells

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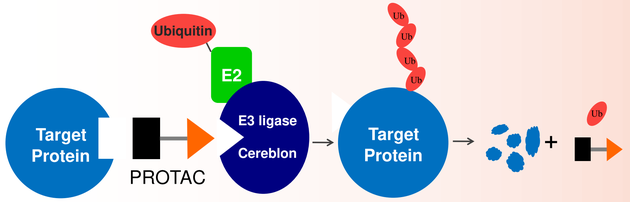
Abstract:

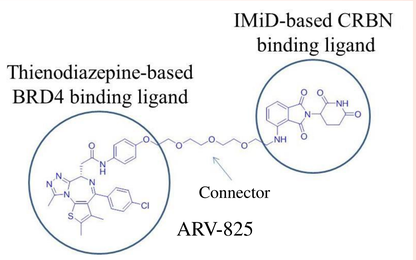
- BRD4, a member of the bromodomain and extraterminal domain (BET) family, has emerged as an attractive oncology target
- BET bromodomain inhibitors have shown promising effects in certain preclinical settings, particularly in c-MYC driven hematological malignancies and prostate cancer
- We designed a Proteolysis Targeting Chimera (PROTAC) compounds (ARV-825, ARV-649), containing a BRD4 binding moiety and a ligand for the E3 ubiquitin ligase cereblon
- BRD4 PROTACs lead to fast and efficient degradation of BRD4 and provides more pronounced and longer-lasting effect in suppressing c-MYC levels than small molecule BRD4 inhibitors
- BRD4 PROTACs are more a effective anti-proliferative and apoptogenic agents in Burkitt Lymphoma, multiple myeloma, and prostate cancer cells compared to BRD4 inhibitors
- BRD4 PROTACs induce regression of AR-V7+ 22Rv1 prostate tumors *in vivo* and appear to provide a better and more efficient strategy in targeting BRD4 than traditional small molecule inhibitors

PROTAC: PROteolysis TArgeting Chimera

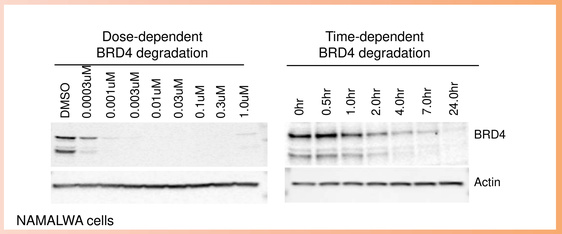


E3 Ligase is recruited to the target protein by PROTAC

Tagged target is recognized and degraded by proteasome

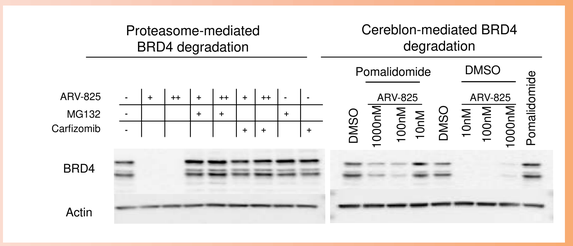


ARV-825 causes rapid and potent BRD4 degradation



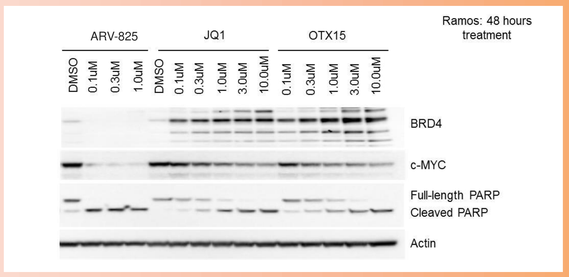
NAMALWA cells

Confirmation of proteasome mediated, cereblon-based mechanism in driving BRD4 degradation by BRD4 PROTAC

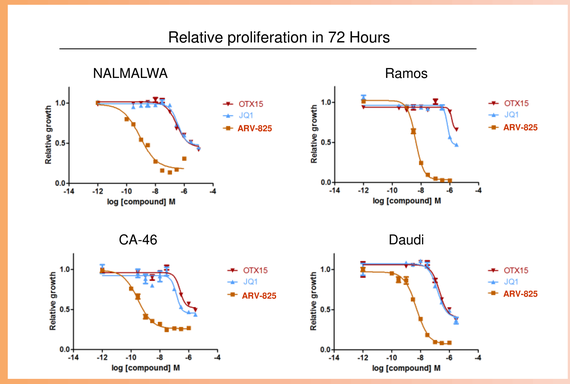


NAMALWA cells, + (10nM), ++ (100nM), MG132 (5uM), Carfizomib (5uM), Pomalidomide (10uM)

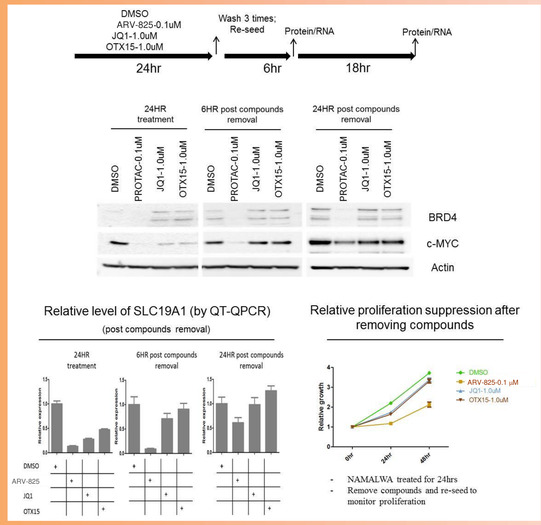
BRD4 PROTAC leads to more significant c-MYC suppression and apoptosis induction than small molecule inhibitors



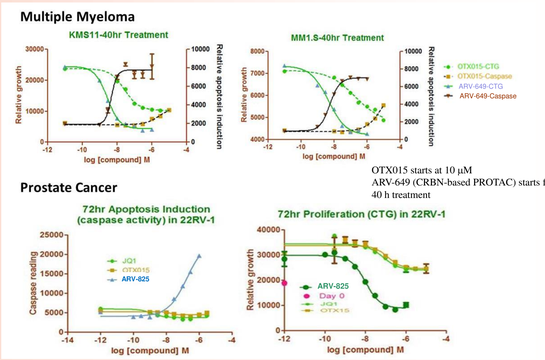
BRD4 PROTAC leads to more significant suppression of BL cell proliferation than small molecule inhibitors



ARV-825 has sustained effects on BRD4 degradation, MYC suppression, Myc downstream signal and proliferation inhibition

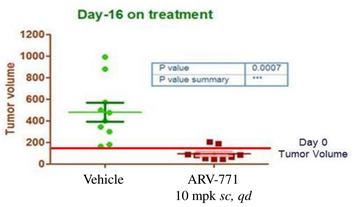


BRD4 PROTACs have greater anti-proliferative and pro-apoptotic activity than inhibitors in multiple myeloma and prostate cancer cells



OTX015 starts at 10 μM
ARV-649 (CRBN-based PROTAC) starts from 1 μM
40 h treatment

BRD4 PROTAC causes regression of AR-V7+ 22Rv1 tumor xenografts



- ARV-771 is a VHL-based BRD4 PROTAC with better bioavailability relative to ARV-825 or ARV-649
- No weight loss was observed during the course of the efficacy study

Summary

- We developed BRD4 PROTACs that degrade BRD4 potently and rapidly
- BRD4 PROTACs cause more significant suppression of c-MYC, more dramatic effect on cell proliferation and apoptosis induction compared to small molecule inhibitors
- BRD4 PROTACs have long-lasting effects on repressing downstream signaling and proliferation
- BRD4 PROTACs cause regression of established 22Rv1 tumors
- PROTAC-mediated degradation of BRD4 provides a more effective strategy in targeting BRD4 than traditional small molecule inhibitors
- Our study demonstrates that PROTAC platform, by actively recruiting E3 ligase to target pathological protein for degradation, is a promising strategy for the development of novel therapeutics