Poster # 2050

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

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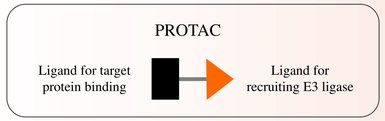
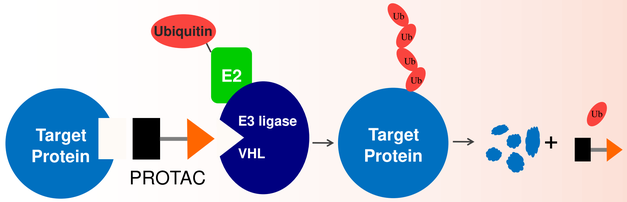
Abstract:

- BRD4, a member of the bromodomain and extraterminal domain (BET) family, has emerged as an attractive oncology target
- BET bromodomain inhibitors have shown promising results in certain preclinical settings, including diffuse large B-cell lymphoma (DLBCL)
- We have designed a Proteolysis Targeting Chimera (PROTAC) ARV-771, a heterobifunctional small molecule containing a BRD4 binding moiety and a ligand for the E3 ubiquitin ligase VHL
- ARV-771 treatment leads to rapid 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 effective in suppressing proliferation and inducing apoptosis in DLBCL compared to BRD4 inhibitors
- BRD4 PROTACs induce profound alterations in signaling molecules crucial for apoptosis in DLBCL

PROTAC: PROteolysis TArgeting Chimera

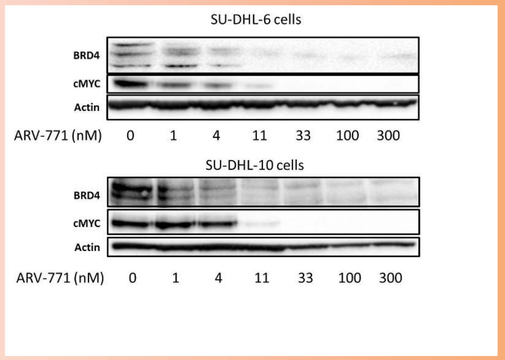




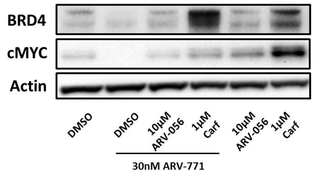
E3 Ligase is recruited to the target protein by PROTAC

Tagged target is recognized and degraded by proteasome

ARV-771 is a potent BRD4 degrader in DLBCL cell lines

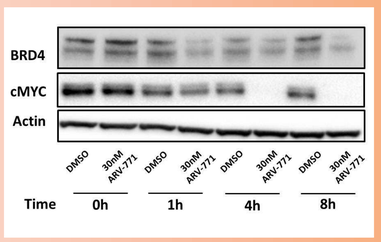


BRD4 degradation by ARV-771 is blocked by pretreatment with an excess of the VHL ligand ARV-056 and with a proteasome inhibitor

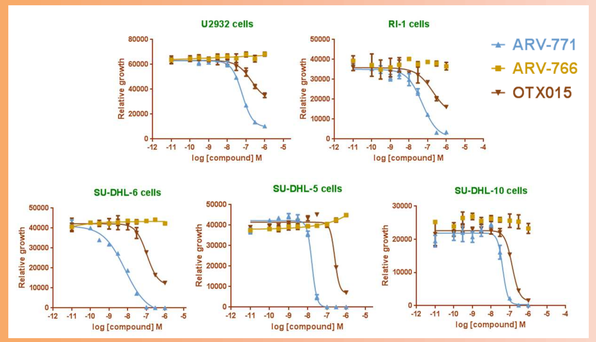


ARV-056 = VHL Ligand
Carf = Carfilzomib (proteasome inhibitor)

PROTAC-mediated BRD4 degradation is rapid, and is achieved within 8h of treatment

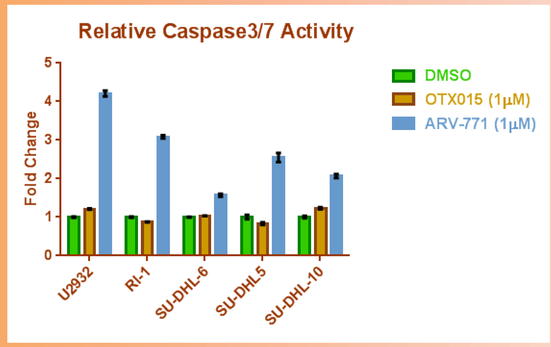


ARV-771 leads to more significant suppression of DLBCL cell proliferation than the BET inhibitor OTX015



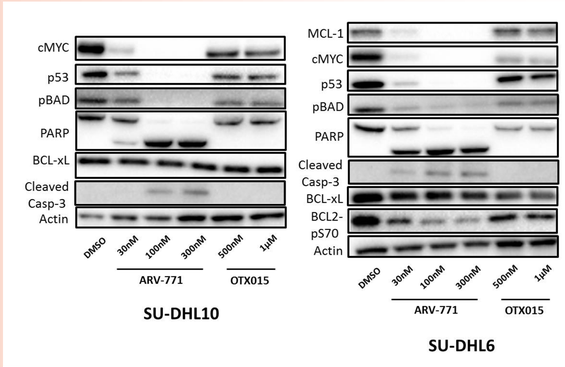
ARV-766, a non-VHL binding diastereomer of ARV-771,has no anti-proliferative activity

ARV-771 leads to more pronounced apoptosis in DLBCL cells than the BET inhibitor OTX015*



* as measured by the Caspase 3/7 Glo Assay (Promega)

ARV-771 induces significant changes of signaling molecules crucial for apoptosis



Summary

- We have developed a BRD4 PROTAC (ARV-771) that degrades BRD4 potently and rapidly
- ARV-771 has significantly greater anti-proliferative and apoptotic activity in DLBCL cells than the BET inhibitor OTX015
- The anti-proliferative effect of ARV-771 is accompanied by profound changes in apoptotic/survival signaling pathways in DLBCL cells
- PROTAC-mediated degradation of BRD4 provides a more effective strategy in targeting BRD4 than traditional small molecule inhibitors
- Our study demonstrates that the PROTAC platform, by actively recruiting E3 ligase to target pathological proteins for degradation, is a promising strategy for the development of novel therapeutics