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.

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

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

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

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 ligases to target pathological proteins for degradation, is a promising strategy for the development of novel therapeutics