Abstract:

- BRD4, a member of the bromodomain and extraterminal domain (BET) family, has emerged as an attractive oncology target.
- BET bromodomain inhibitors have showed promising effects in certain preclinical settings, particularly in c-MYC driven hematologic malignancies.
- Interestingly, we found that BRD4 inhibitors lead to a rapid and robust accumulation of BRD4, which may partially account for their moderate suppression of c-MYC and inhibition of cell proliferation.

We designed a Protolysis Targeting Chimera (PROTAC) compound, containing a BRD4 binding moiety and an E3 ubiquitin ligase domain.

A bromodomain-targeting PROTAC provides more pronounced and longer-lasting suppression of BRD4 than traditional small molecule inhibitors. PROTAC causes rapid and potent BRD4 degradation in driving BRD4 degradation by BRD4 PROTAC

We successfully developed a BRD4 PROTAC that degrades BRD4 potently and rapidly.

BRD4 PROTAC causes more significant suppression of c-MYC, more dramatic effect on proliferation inhibition and apoptosis induction compared to small molecule inhibitors.

BRD4 PROTAC has long-lasting effect on repressing downstream signaling and proliferation.

Targeted degradation of BRD4 by PROTAC provides a better and more effective strategy in targeting BRD4 than traditional small molecule inhibitors.

Our study also demonstrates that PROTAC platform, by actively recruiting E3 ligase to target pathological protein for degradation, is a promising strategy in targeting the “undruggable” proteins by traditional approaches.