Small-Molecule Degrades of the BET Bromodoman Proteins as New Prostate Cancer Therapeutics

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Background: BET Bromodoman Proteins are a class of histone reader proteins and play a key role in regulation of gene transcription. The BET proteins have been considered as attractive new therapeutic targets for advanced prostate cancer and small-molecule BET inhibitors have been shown to be effective in castration-resistance prostate cancer models and in overcoming resistance of AR antagonists. We have developed several classes of highly potent and orally active BET inhibitors.

Methods: Based upon our potent, specific and efficacious BET inhibitors, we have designed and developed several new classes of small-molecule degraders of the BET proteins based upon the proteolysis-targeting chimera (PROTAC) concept. We have performed extensive evaluation of the therapeutic potential and mechanism of action of our most potent and promising small-molecule BET degraders in castration-resistant prostate cancer models.

Results: Our data demonstrate the followings: (a). small-molecule BET degraders are highly potent and effective in inducing degradation of BET proteins in prostate cancer cell lines at low nanomolar concentrations; (2). small-molecule BET degraders are highly potent and effective in suppressing AR signaling; (3). small-molecule BET degraders are highly potent and effective in inhibition of cell growth in prostate cancer cells at low nanomolar concentrations. (4). small-molecule BET degraders are very effective in overcoming resistance of AR antagonists; (5). small-molecule BET degraders are very effective in inhibition of tumor growth in animal models of CRPC in mice at well-tolerated dose-schedules.

Conclusions: Our preclinical data provide strong rationale to evaluate small-molecule BET degraders as a new class of therapy for the treatment of patients with CRPC.

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