Targeting cancer with a novel BET bromodomain inhibitor

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Abstract

Bromodomain and extra-terminal (BET) family proteins are dual bromodomain-containing epigenetic readers that bind to acetylated-lysine residues in histones at gene promoter and enhancer elements and recruit protein complexes to promote transcriptional elongation. Recent evidence demonstrates that BET bromodomain inhibition leads to anti-proliferative activity in pre-clinical models of many hematological malignancies and solid tumors. Selective inhibition of BET bromodomains by small molecule inhibitors has emerged as a promising therapeutic strategy for the treatment of cancer. In this study, we evaluated the antitumor activity of ODM-207, a novel, potent and highly selective BET bromodomain inhibitor.

Methods

Biochemical activity testing of ODM to BRD2, BRD3, BRD4, E1154, KAT2A, MBD2 and MBG full-length recombinant proteins was tested by measuring the displacement of Tetra-acetylated peptides from a solution of biotinylated peptides using streptavidin-coated plates and substrate (p-toluidine blue) or 10% acetic acid and the TRITC assay.

Cell viability and apoptosis assays: Cell line and patient derived cells were treated from pleural effusions or tumor biopsies were grown in standard culture and treated with ODM. Cell viability was assessed using a colorimetric WST-1 assay (Roche, Germany). To detect early apoptosis and necrosis, the cell death detection ELISA Easy kit (Roche, Germany) was performed. To determine the effect of ODM on cell viability, annexin V-PI apoptosis assay kit (Roche, Germany) was used.

Immunofluorescence and cell cycle analysis: Exposure of cells was determined by nuclear and cytoplasmic staining of cells with biotinylated anti-BRD2, BRD3, BRD4, MBD2 or MBD4 antibodies (Abcam, Cambridge, MA, USA) using a streptavidin-AF555 conjugate. To determine the proliferative activity of the cells, the BrdU incorporation assay (Invitrogen) was used. The cell cycle distribution was determined by flow cytometry using propidium iodide staining.

Results

1. Biochemical activity of ODM-207

2. In vitro antiproliferative activity of ODM-207 across multiple tumor types

3. ODM-207 inhibits cell growth and induces apoptosis in a subset of hematological and breast cancer cell lines

4. OTX015 resistant LNCaP prostate cancer cells maintain sensitivity to ODM-207

5. ODM-207 is efficacious as a single agent in xenograft models

Conclusions

ODM-207 is a novel and structurally distinct inhibitor of BET proteins that

• Induces cell cycle arrest and shows broad and potent antiproliferative activity against a wide range of different hematological and solid tumors in vitro and in vivo.

• Induces proliferation of patient-derived cancer cells in comparison with several tumor types.

• Induces proliferation and downregulates Myc levels in prostate cancer cells that have acquired resistance to BET-inhibitor OTX015.

A clinical trial with ODM-207 is ongoing in patients with solid tumors (NCT03035591).