Abstract 4649

ODM-207, a novel BET-bromodomain inhibitor as a therapeutic approach for the treatment of prostate and breast cancer

Mari Björkman 1, Elina Mattila 1, Reetta Rilkonen 1, Chandrasekhar Abbineni 2, Mahaboobi Jalalvi 2, Sivapiya Marappan 2, Tarja Ikonen 1, Daniel Nicorici 1, Juha Rantalä 2, Susanta Samajdar 3, Murali Ramachandra 4, Pekka Kallio 5, Anu Mollanen 1
1Orión Corporation Orion Pharma, Espoo, Finland; 2Autogene Discovery Technologies Limited, Bangalore, India; 3Mark Biologi, Finland

Background
BET [bromodomain and extraterminal] family proteins (BRD2, BRD3, BRD4, and BRD7) are epigenetic readers that bind to acetylated-histone residues in histones and recruit protein complexes to promote transcription elongation. In many cancers, BET proteins have been shown to regulate expression of MYC and other oncogenic drivers that are important for cell proliferation and survival. Pharmacologic inhibition of the BET- histone interaction has been shown to result in transcriptional downregulation of a number of oncogenes and inhibition of tumor growth providing a novel strategy for treatment of cancer. ODM-207 is a novel, potent and highly selective BET bromodomain inhibitor with excellent efficacy in preclinical models of prostate and breast cancer as well as in patient-derived tumor cell cultures from various tumor types.

Methods

1. Bromodomain selectivity profiling: ODM-207 IC50s against BET and non-BET bromodomain proteins were determined using a competitive fluorescence polarization assay. IC50s < 1 nM were considered selective.

2. Tumor growth inhibition: ODM-207 IC50s against xenografts were determined using a modified xenograft assay. IC50s < 25 mg/kg were considered active.

3. Immunofluorescence: Cells were stained with antibodies targeting BET bromodomains and/or MYC and nuclei were stained with DAPI. Confocal images were acquired and cell cycle data was calculated.

4. Immunoblotting: Enrichment analysis (GSEA, Broad Institute).

5. Conclusions: ODM-207 is a novel, potent and structurally distinct inhibitor of BET proteins

Results

1. ODM-207 is a potent and selective BET bromodomain inhibitor

2. Antiproliferative effects of ODM-207 in prostate cancer cell lines

3. Antiproliferative effects of ODM-207 in breast cancer cell lines

4. Antiproliferative effects of ODM-207 in patient-derived cancer cells

Conclusions

- ODM-207
  - Is a novel, potent and structurally distinct inhibitor of BET proteins
  - Inhibits proliferation of prostate cancer cell lines with intact AR signaling in vitro and in vivo.
  - Inhibition of BET proteins leads to induction of senescence and a dose-dependent reduction of Myc mRNA and protein levels in vitro and in vivo.
  - Inhibits proliferation of estrogen sensitive breast cancer cell lines
  - Inhibition of BET proteins is associated with induction of senescence and a dose-dependent reduction of ERα protein levels in vitro
  - Demonstrates dose-dependent inhibition of cell growth in patient-derived cancer cells from various tumor types.