Potential Advantages of CUDC-101, a Multi-Targeted HDAC, EGFR and HER2 Inhibitor, on Preventing Drug Resistance and Tumor Metastasis

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CUDC-101 is a novel small molecule anti-cancer agent targeting HDAC, EGFR, and HER2 currently in Phase Ib clinical trial. Previously, we reported that CUDC-101 has potent anti-proliferative and pro-apoptotic activities in cultured tumor cells and xenograft models when compared to other single target agents. Additionally, we demonstrated that CUDC-101 reduces the levels of both phosphorylated and total MET. In the present study, we demonstrate that cancer cells harboring MET amplification are sensitive to CUDC-101. Because the MET pathway also plays an important role in metastasis, we further investigate the effect of CUDC-101 in regulating cell motility and epithelial-mesenchymal transition (EMT), and demonstrate that CUDC-101 reduces migration, invasion and EMT in vitro. MET amplification and secondary EGFR mutation are two clinically validated mechanisms implicated in EGFR tyrosine kinase inhibitor (TKI) resistance. Erlotinib-resistant, EGFR mutant HCC827R cells are sensitive to treatment with CUDC-101, suggesting that CUDC-101 may be useful for evading common cellular drug resistance mechanisms in cancer.

CUDC-101 inhibits cell migration in HGF- and serum-induced wound healing

CUDC-101 inhibits EMT

Erlotinib-tolerant cells (HCC827R) are still sensitive to the treatment

Introduction

CUDC-101 is a potent inhibitor of HDAC, EGFR and HER2

Cancer cells harboring MET amplification are sensitive to CUDC-101 but not Erlotinib

Conclusions

- NSCLC and gastric carcinoma cells harboring MET amplification are sensitive to CUDC-101
- CUDC-101 suppresses growth factor-induced tumor cell migration, invasion and EMT
- Erlotinib-resistant cancer cells are sensitive to CUDC-101 treatment
- CUDC-101 may be efficacious in simultaneously overcoming tumor growth, metastasis, and drug resistance