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

#2619

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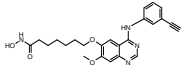
Introduction

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.

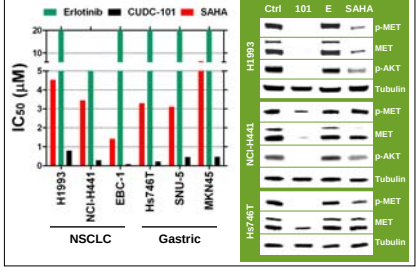
CUDC-101 is a potent inhibitor of HDAC, EGFR and HER2



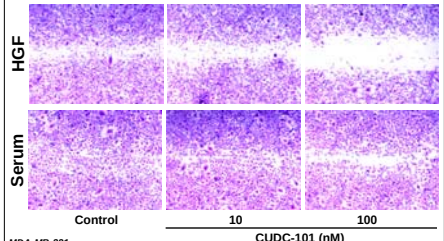
CUDC-101, MW 434.5
HDAC/EGFR/HER2 Inhibitor

Compound	IC50 (nM) in Enzyme Assays		
	HDAC	EGFR	HER2
SAHA	39.1± 4.8	NA	NA
erlotinib	NA	24.6 ± 1.7	146.1 ± 16.4
lapatinib	NA	17.4 ± 8.9	10.6 ± 0.8
CUDC-101	4.2 ± 1.2	2.4 ± 1.7	16.4 ± 2.6

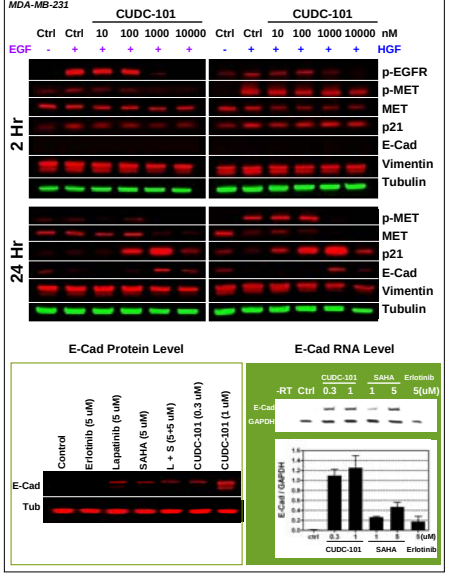
Cancer cells harboring MET amplification are sensitive to CUDC-101 but not Erlotinib



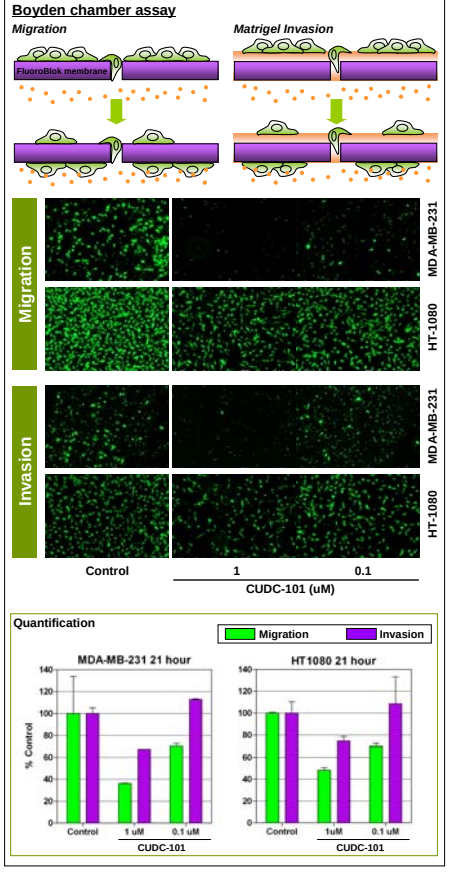
CUDC-101 inhibits cell migration in HGF- and serum- induced wound healing



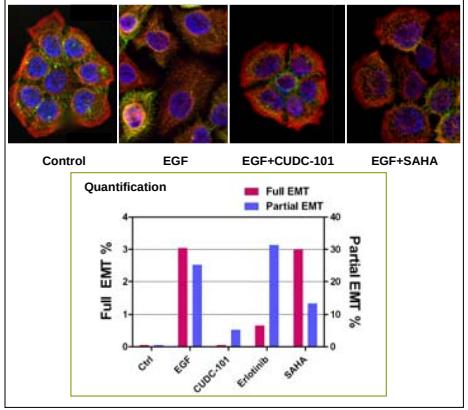
CUDC-101 induces changes in migration markers



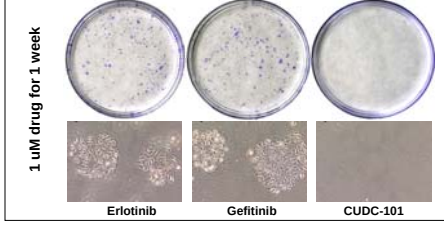
CUDC-101 reduces serum-induced tumor cell migration and invasion



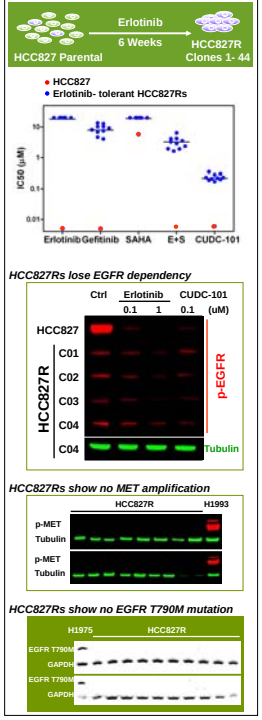
CUDC-101 inhibits EMT



Long-term treatment of HCC827 NSCLC cells with Erlotinib and Gefitinib, but not CUDC-101, produces tolerant cells



Erlotinib-tolerant cells (HCC827R) are still sensitive to the treatment of CUDC-101



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