Conclusions

- CUDC-907 is a dual inhibitor of HDAC and PI3K. It not only inhibits the PI3K-AKT pathway, but also suppresses other vital signaling pathways, and induces apoptosis in cancer cells via epigenetic modification.

- CUDC-907 displays greater anti-proliferation potency against human hematologic cancer cell lines than reference compounds.

- CUDC-907 is orally bioavailable in animals, and displays antitumor activity in PO and efficacy studies in hematologic cancer models with favorable safety profile.

- CUDC-907 disrupts cancer signaling networks, which therefore may overcome limitations of other PI3K-mTOR or HDAC single target inhibitors.

- CUDC-907 was selected as a development candidate.

Rationale and Design of Single Molecule HDAC-PI3K

- Multiple signaling pathways are dis-regulated in cancer. Extensive cross-talk and redundancy exist. Therefore, network disruption is needed to achieve maximum efficacy.

- Blocking PI3K can up-regulate other survival signaling pathways which in turn can be overcome by HDAC inhibition via epigenetic regulation.

- Synergistic effects can be achieved by inhibition of both HDAC and PI3K in cancer cells as reported previously.

CUDC-907 Inhibits Both PI3K and HDAC, and Induces Apoptosis in vitro

- Western blot analysis of Daudi (NHL), 16 Hrs of treatment, 1uM CUDC-907

- Flow cytometry analysis of multiple myeloma cell, 48 hrs of treatment

CUDC-907 Inhibits Tumor Growth in Daudi NHL Models

- Efficacy study in Daudi subQ xenografts

- IHC staining of Ki-67 in CUDC-907 treated Daudi tumor

- PK in tumor-bearing mice 50mg/kg, PO

Conclusions

Antitumor Activity of a Dual PI3K and HDAC Inhibitor in Hematologic Cancer Models

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