Abstract

Endometrial cancer is the most common gynecologic malignancy, causing over 11,000 deaths every year. Progesterone is a key tumor suppressor in endometrial cancer, inhibiting cell growth, promoting apoptosis, and inducing cell differentiation. Existing progestin-based therapy has a low response rate in poorly-differentiated endometrial cancer due to loss of progesterone receptor (PR) expression. The PI3K/Akt/mTOR pathway is hyperactivated in this disease, and it has wide ranging effects on cell proliferation and the cell cycle. Literature reported that targeting the PI3K/Akt/mTOR pathway can increase PR expression. The histone deacetylase (HDAC) is a well studied cancer target which contributes to epigenetic silencing of tumor suppressors in cancer cells. Therefore, we strategized to increase PR expression using a dual PI3K and histone deacetylase inhibitor (HDACi) called CUDC-907. This oral drug is FDA approved in 2015 to treat lymphoma. We plan to test efficacy of CUDC-907 in endometrial cancer to enhance PR expression. Using qPCR, we found that CUDC-907 increases functional PR expression at the mRNA level. We used Western blotting to confirm that CUDC-907 enhances PR expression while inhibiting the PI3K/Akt/mTOR pathway at the protein level. For the next step, we will test it in mice to determine whether CUDC-907 is effective to inhibit endometrial cancer. CUDC-907's dual inhibition strategy shows promise in increasing PR expression to combat endometrial cancer.

Objective

The objective of this study was to investigate the strategy of dual inhibiting PI3K and HDAC using CUDC-907 to increase PR expression. We hypothesize that the dual inhibitors will increase PR expression more than current therapies.

Mechanism

Endometrial cancer cells

PI3K
AKT
mTOR
HDAC
CUDC-907
PGRA
KLE
PR
FoxO1
p21
PGRA/B
Figure 1. CUDC-907 dual inhibits PI3K/Akt/mTOR pathway and HDAC. CUDC-907 inhibits PI3K, downregulating PI3K in AKT and mTOR. PI3K/Akt/mTOR pathway and HDAC, CUDC-907 inhibits HDAC, downregulating HDAC and 4E-BP1. By also inhibiting HDAC, CUDC-907 prevents inhibition of PR expression. This increase in PR decreases the pro-oncogene Myc and increases p21, a cyclin-dependent kinase inhibitor that regulates the cell cycle, and FoxO1, a transcription factor that promotes apoptosis.

Results

CUDC-907 Inhibits Cell Proliferation

Figure 2. CUDC-907 components. CUDC-907 combines the functionality of HDAC inhibitors and PI3K inhibitors to effectively target both pathways. A molecular link joins the functional groups of both inhibitors into a single drug.

Figure 3. CUDC-907 Molecular Structure. With the linkage of the PI3K and HDAC inhibitors, CUDC-907 has both functional groups, allowing its dual inhibitory function.

Figure 4. Varying concentrations of CUDC-907 on cell proliferation in different cell lines. We used Ishikawa cells, ECC1, and KLE cells to assess the effect of different concentrations of CUDC-907 on cell proliferation. Concentrations from 10 nM and above displayed clear reduction in the population of most cell lines with the exception of HeLaS, which only displayed significant reduction at 100 nM of CUDC-907.

Conclusion

- CUDC-907 successfully increases PR expression and inhibits both PI3K and HDAC, showing promise as an effective treatment.
- RNA and protein level analysis confirmed the inhibition of the PI3K/Akt/mTOR pathway, and CUDC-907 produced expected changes in the expression of genes in the pathway.
- Further in vivo studies in mice will determine whether CUDC-907 is an effective treatment for endometrial cancer.

References


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