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Oncology – EZH2 (Enhancer of Zeste Homolog 2) Inhibitor

EZH2 is a histone methyltransferase specific for Histone H3 (K27), and is the catalytic protein of a 5-component protein complex, the Polycomb Repressive Complex 2 (PRC2). EZH2-mediated methylation results in repression/silencing of tumor suppressor gene expression. Numerous studies link the catalytic function of EZH2 and EZH2 over-expression to tumor growth, metastasis, and chemo-resistance. Depletion or inhibition of EZH2 results in suppression of tumor growth and metastasis, and extension of animal survival. Somatic activating mutations of EZH2 resulting in hyper-methylation occur at significantly high frequency in patients with Diffuse Large B-cell Lymphoma. Thus, inhibition of EZH2 is hypothesized to provide a therapeutic benefit in the treatment of cancer.

Compounds of interest will inhibit EZH2 and will be characterized for selectivity against other histone methyltransferases as well as kinases and for evidence of inhibition EZH2 in a cell-based system.

- Chase, A.; Cross, N. C. P. "Aberrations of EZH2 in Cancer," *Clin Cancer Res* 17(9): 2613-8, (2011).
- Sneeringer, C. J. et al. "Coordinated activities of wild-type plus mutant EZH2 drive tumor-associated hypertrimethylation of lysine 27 on histone H3 (H3K27) in human B-cell lymphomas," Proc Nat Acad Sci 107(49): 20980-20985, (2010).

Flow Scheme & Assay Measures

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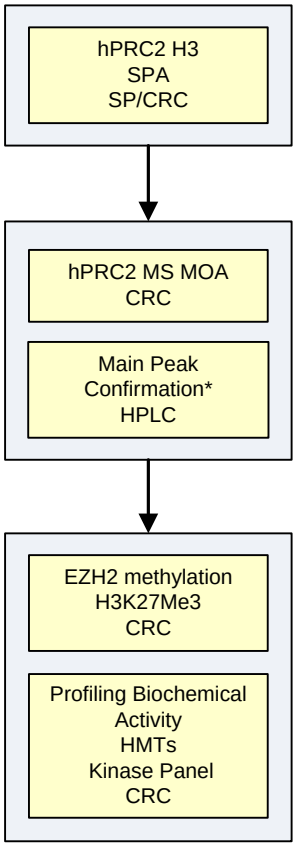

EZH2 Inhibitor (Enhancer of Zeste Homolog 2)

Primary Assays
hPRC2 (EZH2) H3 SPA SP (% Inhibition)**
hPRC2 (EZH2) H3 SPA CRC (IC_{50})**

Secondary assays
hPRC2 MS MOA CRC (IC_{50})
Main peak confirmation HPLC

Confirmatory Assays
EZH2 H3K27Me3 Cell Based CRC (IC_{50})
Profiling Biochemical Activity CRC (IC_{50})

SP= Single Point
CRC= Concentration Response Curve

NOTES:
*** Single Peak purification for active confirmation.**
**** PRC2 is the heteropentameric protein complex that is assayed and EZH2 is the catalytic protein within the complex**