A Novel Approach for Metastatic Breast Cancer Therapy: Pharmacological Inhibition of EZH2 Histone Methyl Transferase Activity Suppresses Cancer Stem Cells and Induces Epithelial Phenotype

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As the leading cause of cancer-related deaths in women worldwide, breast cancer metastasis remains refractory to current therapy. Residing in the Polycomb protein group and altering the chromatin structure, EZH2 trimethylates H3K27 and represses normal tumor suppressor genes. High EZH2 expression levels are associated with increased invasion, metastasis, and poor clinical prognosis. This study evaluated EZH2 inhibition on breast cancer metastasis in aggressive human breast cancer cell lines through an extensive in vitro analysis. Western blots confirmed that blocking EZH2 specifically inhibits H3K27 trimethylation. Scratch assays, invasion assays, and flow cytometry revealed the loss of migration, invasion, and cell proliferation, respectively, post inhibition. Microscopic examination, RT-PCR analysis and immunostaining established the restoration of epithelial marker expression levels. Mammosphere assays, analyzing cancer stem cells, documented decreased cell size and loss of proliferative capacity. Flow cytometry and immunofluorescence identified a reduction in the CD44hi cell population, considered to be the cancer stem cell population. The aldehyde dehydrogenase assay validated the loss of cancer stem cell activity post-EZH2 inhibition. Finally, ChIP-Seq confirmed the increased expression of four critical genes that promote a more benign, less stem-like phenotype. These remarkable discoveries identified EZH2 inhibition as a powerful anticancer agent and uncovered the mechanisms behind EZH2 inhibition-mediated cancer suppression. EZH2 inhibition presents a new therapeutic option to suppress metastasis in breast cancer. Because of its critical role in epigenetic regulation, EZH2 inhibition is a strategy that could be highly effective to treat other metastatic cancers.

Awards Won:
First Award of $5,000