HB007 Administration Inhibits LN-229 and Patient-Derived Neurospheroid Glioblastoma Cell Growth With the Degradation of SUMO1 and Cell Cycle Regulator CDK4

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Background and Hypothesis:

Glioblastoma is the most common and malignant brain cancer and there is no effective therapy currently available to patients with this malignancy. Small ubiquitin-related modifier 1 (SUMO1) is a key regulator of cancer cell proliferation through its role in its modification of cellular proteins in various human cancers, especially glioblastoma. Degradation of SUMO1 through small molecule degrader, HB007, has been shown to inhibit growth in cancer cell lines and xenografts. Here, we hypothesize that HB007 can inhibit the glioblastoma cell growth through degradation of SUMO1 protein in glioblastoma cells and the cancer stem cell enriched neurospheres.

Experimental Design:

LN-229 glioblastoma cell viability was measured in response to increasing concentrations of HB007. LN-229 and patient-derived neurospheroid glioblastoma cells were cultured and seeded in 4 different plates at 1000 cells/ml concentrations before being treated with HB007 at increasing concentrations encircling the previously described IC50. Cells were then subjected to a SUMO lysis buffer and analyzed via western blot with antibodies specific to SUMO1, CDK4, and actin.

Results:

HB007 treated LN-229 cells exhibited an IC50 of 1.470μM. Western blot analysis confirmed the dose dependent reduction in SUMO-1-ylated proteins in HB007 treated cells. A reduction in CDK4 confirmed that cell progression is halted in a dose dependent manner in LN-229 and patient-derived neurospheroid glioblastoma cells when treated with HB007. Specificity of HB007 is towards SUMO1 with no nonspecific degradation of SUMO2/3.

Conclusion:

The cell growth of LN-229 and patient-derived neurospheroid glioblastoma cells was confirmed, through western blot, to be inhibited in a dose dependent manner by HB007. These results further establish the therapeutic potential of SUMO1 degraders as a novel anticancer drug for glioblastoma therapy. In the future, it is hoped that the bioavailability, potency, and blood brain barrier permeability can be improved to make this drug a potential treatment for patients.