**Anti-proliferative effects of HDAC8 PROTAC on HSCC cells via endoplasmic reticulum stress**

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**Introduction.** Hypopharyngeal squamous cell carcinoma (HSCC) has a high mortality rate. HDAC8, an enzyme that catalyzes the deacetylation of histone and non-histone proteins, plays a role in cancer progression. HDAC8 is overexpressed in oral squamous cell carcinoma (OSCC). We hypothesized that HDAC8 level is associated with the progression of HSCC. Proteolysis targeting chimera (PROTAC) proteins degrade specific proteins; therefore, it has significant advantages over conventional protein inhibitors. PROTAC can suppress all functions of targeted proteins because it degrades targeted proteins from the cell. The preliminary data on cell viability of HDAC8 PROTAC using MTT assays showed the IC50 against FaDu cells is approximately 1.202 µM. Therefore, we selected the concentrations
0.5 and 2.5 µM, the lower and higher concentrations than the IC50 value, to determine cell proliferation activity.

**Aims**. We compare the prohibition of cell proliferation and endoplasmic reticulum stress (ER) stress markers of HDAC8 PROTAC, HDAC8 inhibitor, Vorinostat (SAHA), Pomalidomide and Cisplatin on FaDu cell line.

**Methods**. FaDu cells were stained with Deep Red staining and the percentage of mean fluorescence intensity (MFI) was measured by flow cytometry. The increase in MFI indicates the inhibition of cell proliferation. The expression of ER stress marker mRNA was measured using real-time PCR.

**Results.** The percentage of mean deep red intensity of FaDu after exposed to HDAC8 PROTAC is 10 times higher than HDAC8 inhibitor and 5 times higher than SAHA under the same concentration of 2.5 µM for 72 h. Real-time PCR shows increased ER stress-related genes such as XBP1s, CHOP, and ATF4 after exposed to HDAC8 PROTAC.

**Discussion.** HDAC8 PROTAC inhibits cell proliferation and induces ER-stress gene expression. Taken together, the present study shows that HDAC8 PROTAC is a potent therapeutic agent for HSCC.