Targeted Degradation of EZH2 leads to Reduced Tamoxifen Resistance in ER-Positive Breast Cancer

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Approximately 70% of all breast carcinoma cases are Estrogen Receptor Positive, and are commonly treated with aromatase inhibitors or selective estrogen receptor modifiers such as Tamoxifen.

Proteolysis Targeting Chimeras ( PROTACs) are small molecules that can bind a protein of interest (POI) and facilitate its degradation. Recent studies have found that PROTACs may also facilitate the degradation of factors that associate with the POI as well.

Because EZH2 is known to interact with ER-signaling and associate with oncogenic transcription factors, a PROTAC targeting EZH2 could facilitate downregulation of estrogen responsive genes in ER+ breast cancers, and could interfere with pathways conferring Tamoxifen resistance.
Visualization of Growth Inhibition in Estrogen Receptor Positive Breast Cancer Cells treated with MS177 or MS8815 PROTAC, and Dependence on Tamoxifen

The MS177 PROTAC (blue) is more effective at inhibiting growth of the T47D-TR cells than the MS8815 PROTAC (purple). Both PROTACs inhibit growth in a dose-dependent manner.

The MS8815 PROTAC (red) inhibits growth of the MCF7-TR cells in a dose-dependent manner, but the MS177 PROTAC does not appear to inhibit growth. Moreover, growth inhibition by MS8815 is less significant than the inhibition seen by MS177 in the T47D-TR cells.

The MS177 PROTAC sensitizes the T47D-TR cells to Tamoxifen in a dose-dependent manner.

Tamoxifen does not appear to significantly inhibit growth of the T47D-TR cells.

The MS177 PROTAC sensitizes the Tamoxifen resistant (TR) ER+ T47D cells to Tamoxifen in a dose-dependent manner. Further, this PROTAC facilitates degradation of EZH2, correlating with downregulation of estrogen receptor (ER) and oncogenic transcription factors. Finally, treatment of these ER+ breast cancer cells with MS177 correlates with downregulation of estrogen responsive genes and genes correlating with Tamoxifen resistance (data not shown). In contrast, the MS8815 PROTAC appears to inhibit growth of the ER+ TR-MCF7 cells alongside degrading EZH2 and downregulating ER and oncogenic transcription factors, but MS177 does not appear to have an effect in these cell lines. These data suggest possible differences in the canonical H3K27me3 and non-canonical (oncogenic transcription factor and co-activator activation) activities of EZH2 in ER+ breast cancers.

While the MS177 PROTAC appears effective in reducing Tamoxifen resistance in T47D cells, further investigation into the differences that these PROTACs have on different ER+ cell lines will be necessary in developing a therapeutic for treatment of a heterogenous ER+ breast cancer tumors in-vivo.