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"The efficacy of RJ-22, RJ-23, and AT-13 against the MCF7-Y537S mutation of ERa-positive breast cancer cells"

Estrogen receptor alpha (ERa) is expressed in about 70% of breast cancers. ERa binds estrogens and functions as a driver for growth in the tumor and leading to metastatic tumors. ERa breast cancer cells are treated with endocrine therapies. Endocrine therapies include selective estrogen receptor modulators (SERMs) that bind to ERa, thereby blocking estrogen from binding, selective estrogen receptor degraders (SERDs) that bind to ERa and degrade the estrogen receptor, and aromatase Inhibitors (AIs) that block aromatase, which produces estrogen from androgens. Although these methods are effective at combating these breast cancer cells, in approximately 20% of cases, the cells will mutate, leading to a cancer cell that no longer requires estrogen binding and is resistant to current ERa targeting therapeutics. These mutations are occasionally found in the primary tumor of ERa+ cancer but are mostly found in metastatic tumors. Endocrine therapies target ERa, leading to the degradation of proteins. What makes this mutation difficult to deal with is its activity without estrogen, and no known effective strategies for these mutations. Y537S is the most common mutation, accounting for around 60% of mutated cases. This mutation is formed in the ligand binding domain where the tyrosine (Y) is replaced by serine (S) at position 537.

Previously in this lab, it was determined that the compounds RJ-22, RJ-23, and AT-13 have shown efficacy in reducing the proliferation of wild-type Michigan Cancer Foundation-7 (MCF-7) breast cancer cells by decreasing the transcription of ERα genes, resulting in a reduction of mRNA and ERα protein. Therefore, drugs like RJ-22, RJ-23, and AT-13 could be applied to this mutant cancer cell. In MCF7-Y537S change of tyrosine to serine at the 537 position in ERa makes the receptor constitutively active in the absence of the ligand estrogen. In this lab, it was determined that the compounds also inhibit cell proliferation in MCF7-Y537S cells. To determine whether the mechanism is identical to that of the WT MCF7 inhibition, we performed western blot analysis and qRT-PCR assay to determine the ERa levels in the mutant cells. The results from the experiments will be presented here.