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"Development of PDE10A Inhibitor for the treatment of Triple Negative Breast Cancer"

Triple-Negative Breast Cancer (TNBC) is the most aggressive form of breast cancer, and it accounts for about 15-20% of all breast cancer cases. Patients with TNBC have the highest likelihood of metastasis and relapse. Unlike most breast cancers, TNBC is negative for Estrogen, Progesterone, and HER2 receptors which makes it difficult to treat with targeted therapies. The only effective therapies are chemotherapy and radiation which have debilitating side effects. Due to these limitations, existing therapies either need to be improved or new therapies need to be developed.

PDE10A is an enzyme that regulates intracellular signaling by degrading cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). In many TNBC cases, overexpression of PDE10A leads to the activation of signaling pathways, such as the Ras-MAPK pathway, that are responsible for aggressive cell proliferation and metastasis. These findings make PDE10A a potential therapeutic target for treating TNBC. Considering the current therapeutic role of PDE10A inhibition, Dr. Gary Piazza and his colleagues (Auburn University) have developed and characterized a novel PDE10A inhibitor named compound Y (due to patenting issues, the exact name and chemical formula of the compound is kept unknown and we will use the compound name as Y from hereafter). Using the Kaplan Meier Plot, we found a higher expression of PDE10A in TNBC patients, and we confirmed overexpression of PDE10A in TNBC cell lines. In our current study, we evaluated the effects of compound Y on TNBC cells. We performed MTT assays, colony forming assays, apoptosis assays, and mammosphere formation assays.

Our results indicated that compound Y significantly inhibited TNBC cell proliferation and colony forming ability in dose-dependent manners. Further, compound Y significantly induced apoptosis in TNBC cells. We also analyzed the effects of compound Y on *in vitro* tumor models, mammospheres. The results demonstrated that compound Y significantly inhibited mammosphere growth in dose-dependent manners with an $IC_{50\ of}$ approximately 0.45 μM. Considering our current results, we may conclude that compound Y seems to be a promising candidate for targeting TNBC. However, further studies are needed to evaluate the mechanisms of compound Y and its applicability with other therapies such as chemo- and immunotherapies.