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"Targeting the Notch Transcriptional Pathway: A Potential Therapeutic Approach for Triple-Negative Breast Cancer"

Background: Triple-negative breast cancer (TNBC) is an aggressive and heterogeneous form of breast cancer that lacks expression of estrogen, progesterone, and human epidermal growth factor receptor 2. TNBC accounts for 10-15% of all breast cancer cases and is associated with poor prognosis. Notch signaling is up-regulated in TNBC and plays a pivotal role in mediating therapy resistance and cancer-stem cell (CSC) survival. Limantrafin [(CB-103, Cellestia Biotech), Selleckchem], a first-in-class oral transcriptional Notch inhibitor, selectively blocks the interaction between the CSL-NICD complex and leads to transcriptional downregulation of the Notch oncogenic pathway. Phase 1 clinical trials conducted by Cellestia Biotech on the effect of CB-103 on adenoid cystic carcinoma and T-cell acute lymphoblastic leukemia have shown promising safety profiles and efficacy. In preclinical models, CB-103 was also shown to synergistically act with several anti-neoplastic agents to inhibit tumor progression and delay relapse. Here, our aim is to investigate further and characterize the effect of CB-103 on TNBC *in vitro* and *in vivo* using a syngeneic mouse model to understand tumor-immune interactions.

Methods: Two different human TNBC cell lines, MDA-MB-231 and MDA-MB-468, were used for our experiments. MTT and colony forming assays were performed to assess cell viability and proliferation after treatment with increasing concentration of CB-103. Flow cytometry analysis was performed to quantify whether CB-103 induces apoptosis. Mammosphere formation assay was performed to interrogate CSC activity using CB-103 alone and in combination with paclitaxel (FDA-approved chemotherapy). T cell proliferation assay was performed to assess the effect of CB-103 on T cell functions. FVB mice (female) bearing the syngeneic TNBC (C0321) tumors were treated with CB-103 (50 mg/kg BW, PO, daily) over 14 days to analyze the effect on tumor growth.

Results: CB-103 was shown to significantly decrease TNBC cell proliferation and colony formation in a dose-dependent manner. Flow cytometry analysis revealed that CB-103 induces TNBC apoptosis. CB-103 alone and in combination with paclitaxel significantly reduced mammosphere formation. CB-103 does not decrease T cell proliferation. CB-103 significantly reduced syngeneic mouse TNBC tumor growth without a change in body weight.

Conclusion: Our results indicate that CB-103 has potent anti-tumor activity without adverse effects on the immune system. Further investigation is warranted to completely understand the interaction between the tumor and the immune microenvironment in the presence of CB-103. Overall, this study will significantly increase our knowledge to design a clinical trial for TNBC with a novel therapeutic agent, CB-103.