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

Jasjeet Singh, Mrityunjoy Biswas, Md. Manirujjaman, and Fokhrul Hossain
Department of Genetics, Louisiana State University Health Sciences Center – New Orleans; LSU LCMC Cancer Center

Introduction

- Triple-negative breast cancer (TNBC) is an aggressive and heterogeneous form of breast cancer
- Notch signaling is a key pathway for cell differentiation, proliferation, and apoptosis in TNBC. Notch signaling is up-regulated in TNBC and plays a pivotal role in mediating therapy resistance and cancer-stem cell 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

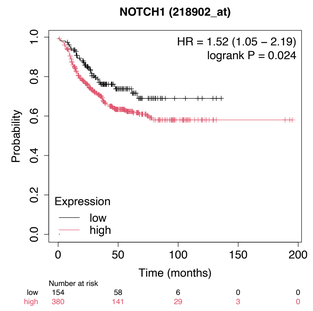

Figure 1. Kaplan-Meier Plotter Analysis for Notch1 in TNBC.

Objective

- We aim to investigate the effect of CB-103 on TNBC *in vitro* and *in vivo* using a syngeneic mouse model to understand tumor-immune interactions

CB-103 inhibited TNBC proliferation

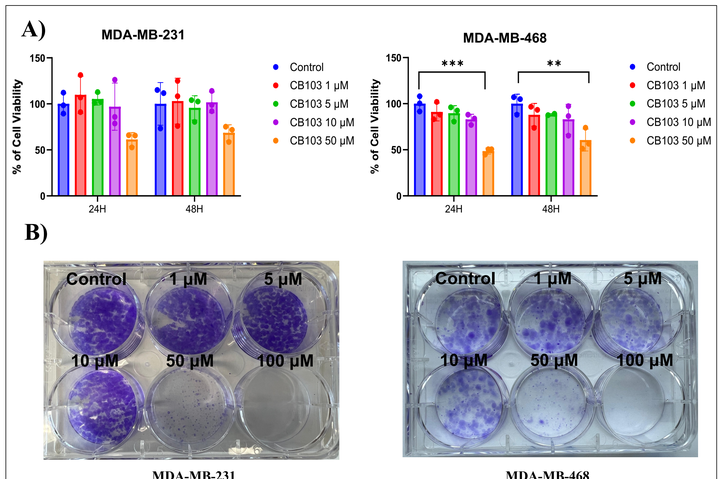

Figure 2. A) MTT and **B)** colony formation assays were performed to assess cell proliferation and viability. CB-103 inhibits cell proliferation and colony formation in two different human TNBC cell lines, MDA-MB-231 and MDA-MB-468, in a dose-dependent manner.

CB-103 induced TNBC apoptosis

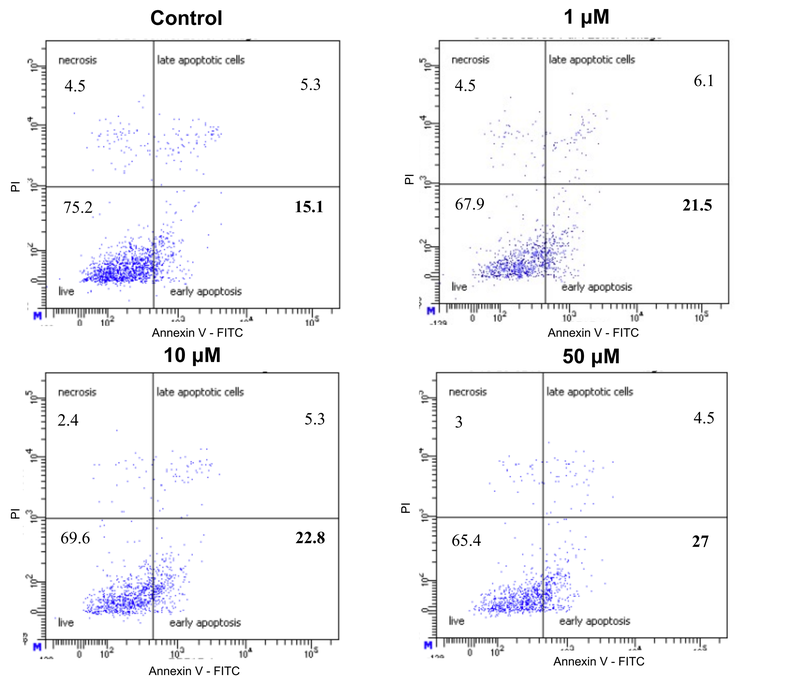

Figure 3. Flow cytometry analysis of MDA-MB-231 cells treated with CB-103 at varying concentrations. Cells were stained with Annexin V-FITC and PI to distinguish live (Annexin V-, PI-), early apoptotic (Annexin V+, PI-), late apoptotic (Annexin V+, PI+), and necrotic (Annexin V-, PI+) cells.

CB-103 inhibited mammosphere formation

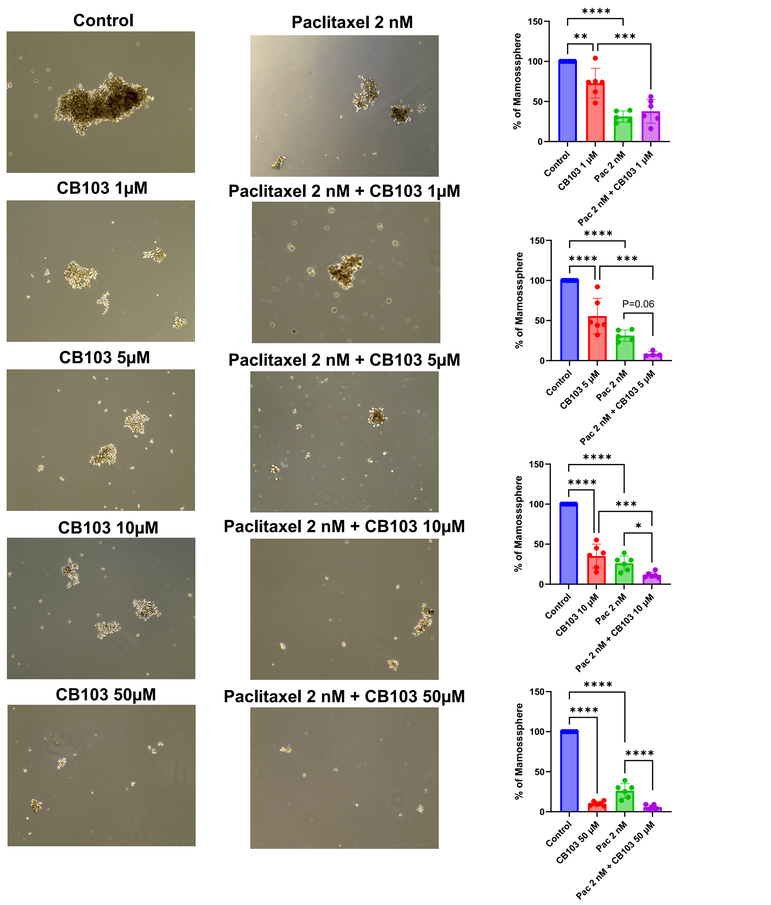

Figure 4. Mammosphere formation assay of MDA-MB-231 cells treated with CB-103 alone and in combination with paclitaxel, an FDA-approved therapeutic agent for TNBC. P1 mammospheres were counted on day 7.

CB-103 is not cytotoxic to T cells

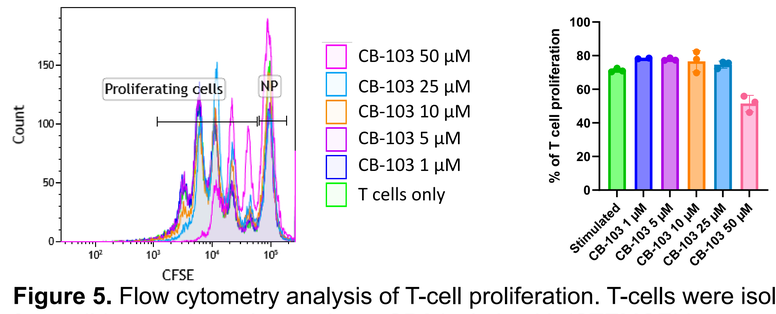

Figure 5. Flow cytometry analysis of T-cell proliferation. T-cells were isolated from wild-type mice spleen using a CD3 isolation kit (STEMCELL Technologies). T-cells proliferation was performed on plate bound anti-CD3 and anti-CD28 antibody in the presence of varying concentrations of CB-103. T-cell % proliferation was measured after 72 hours by CFSE dilution.

CB-103 suppressed TNBC syngeneic tumor growth

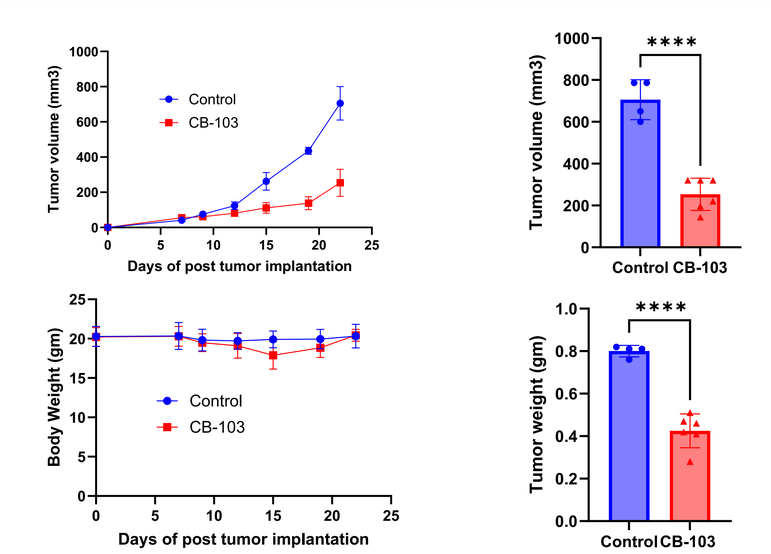

Figure 6. FVB mice (female) bearing the syngeneic TNBC (C0321) tumors were treated with CB-103 (50 mg/kg BW, PO, daily) over 14 days to analyze the effect on tumor growth. CB-103 significantly decreased tumor volume without a change in body weight.

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

References

Vigolo M, Urech C, Lamy S, Monticone G, Zabaleta J, Hossain F, Wyczechowska D, Del Valle L, O'Regan RM, Miele L, Lehal R, Majumder S. The Efficacy of CB-103, a First-in-Class Transcriptional Notch Inhibitor, in Preclinical Models of Breast Cancer. Cancers (Basel). 2023 Aug 3;15(15):3957. doi: 10.3390/cancers15153957. PMID: 37568775; PMCID: PMC10416998.