Susan G. Komen
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BET bromodomain proteins as novel therapeutic targets in TNBC

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Public Abstract:
Triple negative breast cancer (TNBC) is a major subtype of the disease characterized by the lack of estrogen receptor (ER), progesterone receptor (PR) expression and human epidermal growth factor receptor 2 (HER2) activation. TNBCs have a high rate of recurrence to distant metastatic sites and is currently the only major subtype of breast cancer that lacks targeted therapies. Largely due to this, unfortunately a significant fraction of patients diagnosed with TNBC die of their disease within five years of diagnosis. Thus, new treatment options are needed. Cancer is fueled by changes in the DNA sequence (mutation) of genes that regulate cell growth and death, making mutant genes excellent therapeutic targets. Unfortunately in TNBCs no new commonly mutated genes has been found. Thus, the identification of novel therapeutic targets in TNBCs requires other approaches. Each cell in our body has the same DNA sequence, yet has very different properties, which is determined by epigenetic programs that involve modification of DNA and proteins wrapped around it (i.e., chromatin). Cancer cells frequently loose their cellular identity due to perturbed epigenetic programs. Thus, epigenetic regulators are emerging therapeutic targets. One group of such regulators is the BET bromodomain proteins with BRD4 as representative member. Inhibitors of BET bromodomain proteins (BBDIs) stop the growth of some cancer types. I have found that BBDIs significantly growth inhibited TNBC cells and patient-derived TNBC tumors in immunodeficient mice, and that the mechanisms of this is different than that in other cancer types. I have developed BBDI resistant TNBC cell lines. Based on my preliminary data, I hypothesize that the targets of BBDIs in TNBCs remain to be identified and that BBDIs represent novel therapeutic agents in TNBCs. I propose two specific aims to test these hypotheses: Aim 1: I will identify and characterize the targets of BBDIs in TNBCs by analyzing the gene expression and chromatin profiles of cells before and after BBDI treatment. I will integrate these two types of data and identify key changes that correlate with response to treatment. I will utilize TNBC cell lines and patient samples for these studies. Aim 2: I will characterize resistance mechanisms to BBDIs and define ways to overcome them. Understanding this resistance mechanism will help me identify the key targets of BBDIs in TNBCs. I will analyze TNBC cells that developed resistance to BBDIs using the same methods as in Aim 1 and compare these results to that obtained from sensitive cells. I will also conduct a screen to identify compounds that enhance the growth inhibitory effects of BBDIs in TNBCs and overcome resistance. My results will facilitate the design of clinical trials by helping the selection of patients who will most likely respond to BBDIs and by suggesting effective drug combinations. This project will be a great learning experience for me in translational breast cancer r