



Susan G. Komen

Research Grants – Fiscal Year 2015

This research grant was approved for FY2015 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Triple negative breast cancer: subtypes, molecular targets, and therapeutic approaches

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Lead Organization: Vanderbilt University

Grant Mechanism: Komen Scholars

Grant ID: SAC110030

Public Abstract:

Women with tumors that lack HER2 amplifications and estrogen or progesterone receptors, that are overrepresented in BRCA1 mutation carriers and in the African-American population, do not benefit from the current targeted therapies. These difficult-to-treat cancers are classified molecularly as triple-negative breast cancers (TNBC). Long-term follow-up on TNBC patients has shown that these individuals have an increased likelihood of distant recurrence and death compared to women with other types of cancer. There is an urgent need to create targeted therapies for patients diagnosed with TNBC. This can only be accomplished if faster, more efficient methods are developed to convert genetic information into new targeted therapies. From our recent integrated genomic analyses accomplished during the last two years of our Komen-funded research grant, we discovered that TNBC can be classified into six subtypes, each with distinct biologically relevant signaling pathways that drive tumor cell growth. Further, we identified 25 TNBC cell lines representative of these subtypes. Predicted 'driver' signaling pathways were pharmacologically targeted in these cell lines as proof of concept that analysis of distinct genomic signatures can inform therapy selection. Translating this pre-clinical work continues to be the overall aim of the current proposal. Our ongoing hypothesis is that an innovative combination of genomic data mining, molecular biology, and laboratory model systems can be used for streamlined 'target' identification within pathways that drive different types of TNBC; and, these pathways can be targeted for therapeutic benefit for patients and result in much more individualized, precision care for each TNBC patient. Common features of the majority of TNBC tumors is the inability of the tumor cells to repair DNA damage and the dependency of the tumor cells on 'robust' growth signals that come from



a pathway referred to scientifically as the PI3K pathway. This continuation proposal will focus on analyzing the tumor tissue from patients enrolled in a novel clinical trial to determine if a set of genomic markers can predict sensitivity or resistance to the drugs tested in the trial, BRE1287. The trial is focused on evaluating the efficacy of cisplatin (a DNA damaging agent to which TNBC cells are very sensitive) and GDC-0032 (PI3K inhibitor from Genentech) versus cisplatin alone in patients with metastatic TNBC. This trial is based on our preclinical data generated in the past funding period. The trial will also test our ongoing hypothesis and importantly let us understand why specific patients will respond to the treatment and why other don't; and for the latter find better methods to target their tumors. The ultimate outcome of the proposed research is to successfully advance data from the laboratory to the clinic in the form of rationale, target-driven clinical trials as well as discover additional candidate targets as 'leads' for future investigation.

