



**Susan G. Komen
Research Grants – Fiscal Year 2014**

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Targeting DNA damage responses in breast cancer

Investigator(s): Kareem Mohni, Ph.D.; David Cortez, Ph.D. (Mentor)

Lead Organization: Vanderbilt University Medical Center

Grant Mechanism: PDF Basic and Translational

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Public Abstract:

Currently triple negative breast cancer (TNBC) accounts for 25% of breast cancer deaths. Mutations in DNA repair genes are frequent in TNBC and genomic studies indicate significant genome instability in a subset of TNBC suggesting defects in DNA repair. The goal of my research is to understand the mechanisms that control DNA repair in breast cancer and to use that knowledge to create novel cancer treatments. I am especially interested in validating the use of small molecule inhibitors of the protein ATR. This protein is a key node in the cellular response to DNA damage and we hypothesize that it will be a good target in TNBC as well as other cancers since they have an elevated requirement for its function to grow and survive. Aim 1 of the proposal examines a specific genetic interaction with the ATR drug and to understand the basic biological mechanisms explaining this interaction. Aim 2 aims to identify additional genetic interactions. I expect that the results of these studies will provide pre-clinical data to select patients for clinical trials of ATR-targeted drugs who are most likely to benefit from it. There are several drug companies actively developing these drugs so I expect my results to provide important information on how it kills cancer cells and where it might be most effectively deployed to benefit patients. The results will also further our understanding of how cancer cells detect and repair problems in DNA and which pathways we should target for treatments. My career goals are to become a successful scientist at a major academic medical center. My lab will focus on basic and applied principles of genomic stability and DNA damage response to better understand how these pathways function and how this knowledge can be exploited for the creation of novel cancer therapies. I will acquire a foundation of knowledge in breast cancer biology by engaging in focused research under the guidance of Dr. David Cortez. Dr. Cortez is the leader of the Genome Maintenance Program within the Vanderbilt-Ingram Cancer Center (VICC) and a participant in the VICC Breast SPORE. The Cortez laboratory, in collaboration with other Vanderbilt Investigators, is actively studying the DNA damage response in TNBC and has a grant to target the DNA damage response with small molecules for cancer therapy. I have designed a rigorous training program which will help me to refine my ability to conduct independent hypothesis-driven research, to expand my knowledge base, broaden my research skills, and sharpen my ability to think critically. I will acquire a foundation of knowledge in molecular cancer biology by engaging in research under the guidance of Dr. David Cortez. I will expand my technical background with training in biochemistry and molecular biology. Finally, I will attend seminars, journal clubs and meetings on breast cancer research to obtain the background needed to identify where my research should be targeted for maximum impact.