



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

This research grant was approved by Komen's national board of directors for FY2014 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

A novel protein complex controls homologous recombination repair in breast cancer

Investigator(s): Jingsong Yuan, M.D., Ph.D.

Lead Organization: UT M.D. Anderson Cancer Center

Grant Mechanism: CCR Basic and Translational

Grant ID: CCR14302299

Public Abstract:

All of the genetic information is stored in DNA of a cell. Human cells are continuously challenged by both normal metabolic activities and environmental factors such as UV light and radiation, which will result in extensive DNA damage in every cell every day. DNA double-strand break (DSB) is one of the most severe DNA lesions, in which both strands in the DNA double helix are severed. Two mechanisms exist to repair DSBs: non-homologous end joining (NHEJ) and homologous recombination (HR). While NHEJ directly joins the two DNA ends, HR requires the presence of an identical sequence to be used as a template for repair of the break. Therefore, HR is particularly important for the repair of DSBs due to its ability to accurately restore genetic information. Genomic instability and ultimately initiation of tumorigenesis could occur due to inefficient or inaccurate repair of DSBs. HR machinery contains a number of HR factors including the famous BRCA1 and BRCA2 tumor suppressors. Deficiencies in HR have been strongly linked to cancer formation in humans, especially breast cancer. The mutations and malfunctioning of BRCA1 and BRCA2 have been linked with increased risk for breast and ovarian cancer. Cells with BRCA1 or BRCA2 mutations have a decreased rate of HR and increased sensitivity to ionizing radiation, suggesting that decreased HR leads to increased susceptibility to cancer. Although we know a lot about familial breast cancer and developed effective treatment regimens based on HR deficiencies in patients with BRCA1 or BRCA2 mutations, the development of sporadic breast cancer, which is more common, is still largely unknown. Our research questions in this proposal include whether there are yet-to-be-identified HR factors that are functionally inactivated in sporadic breast cancers, whether deficiency in these new HR factors can be used to identify breast cancer patients who would benefit from treatments including PARP inhibitors, and whether these new HR factors can be targeted directly for breast cancer therapy. Using a series of complementary approaches including generating genetically modified mice, we will reveal a set of novel HR factors, deficiencies in which will impair HR repair and result in breast cancer development. Our long-term goal is to discover biomarkers in sporadic breast cancer with HR defects, and help to identify a larger proportion of sporadic breast cancer patients, who may benefit from the treatment regimens designed for familial-BRCA tumors.