

**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.

**The role of RAGE-ligand signaling in breast cancer progression and metastasis**

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**Lead Organization:** Indiana University (Indianapolis)

**Grant Mechanism:** CCR Basic and Translational

**Grant ID:** CCR15333233

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**Public Abstract:**

“Epigenetics” is a study of the changes to gene activity without changing DNA sequences in the growth (or development) of an organism, in this case, breast cancer. In addition to research on how best to diagnose and treat all the various cancers, the moment that cancer begins (carcinogenesis) is an equally important area. This project pursues cancer by way of being able to identify epigenetic changes that indicate cancer will most likely begin. If science can fully understand what to look for, then effective therapies can be developed in response.

“DNA methylation” is a key epigenetic mechanism. The term describes the biochemical process where a methyl group attaches to specific DNA sequences called CpG sites or “islands.” (“CpG” stands for Cytosine-phosphate-Guanine: two of the four nucleotides that make up DNA, connected by a single phosphate.) DNA methylation is critical to cancer research because abnormalities in it can turn on oncogenes, the genes responsible for the uncontrolled growth of tumors. DNA methylation can also turn off, or “silence” tumor suppressor genes. When science is able to identify the how, why, and when of carcinogenesis, the battle will be won.

Such causal alterations in DNA methylation occur early in breast cancer development or even in normal breast long before tumor diagnosis. More importantly, alterations in DNA methylation, unlike alterations in DNA sequence, are reversible. Thus causal DNA methylation markers are attractive candidates for the development of early predictive biomarkers and new therapeutic targets. Identifying these casual DNA methylation markers remains a major challenge in breast cancer research. Most research in this area cannot distinguish the DNA methylation markers that cause breast cancer from those that are the consequences of the disease.

In this proposal, identifying the DNA methylation markers that cause breast cancer will be done using a novel, integrative genomic and epidemiological approach. The project will investigate how DNA methylation markers are altered in normal breast cells by genetic susceptibility factors (mutations in

DNA sequence) versus environmental risk factors (reproductive history, lifestyle, and dietary factors). How are these changes linked to breast cancer initiation and progression? Answering these questions will help prevent cancer.

Because DNA methylation markers change in response to breast cancer-related environmental exposures, such as alcohol intake or hormone use, such DNA methylation markers can also be used as benchmarks to evaluate dietary and lifestyle interventions. The expected outcome of this project is identifying causal DNA methylation markers that drive breast cancer development. When science fully understands how oncogenes begin, it will pursue having them never turn on. That is cancer prevention. In this particular case, breast cancer, but it would apply to many, if not all, cancers.