



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

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Regulation of metastasis by mitochondrial DNA

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Lead Organization: University of Kansas Medical Center Research Institute

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Public Abstract:

More than 90% of cancer related morbidity (the complications associated with cancer, such as pain, weight loss, bleeding, impairment of normal organ function) and mortality (death) are directly attributable to the spread of cancer to nearby or distant secondary sites within the body. Cancer spread and colonization is termed metastasis. The proposed research is designed to answer three fundamental questions and is organized into three projects. Project #1 asks the question: Why do metastases develop in some people, but not others, with otherwise equivalent risk factors? Some people develop cancer while others – with the same behaviors and risk factors – do not. Likewise some patients develop metastases while others do not despite being apparently equivalent. For example, African-American patients with breast cancer or prostate cancer frequently develop more aggressive disease than their Caucasian counterparts. While Project #1 is the primary focus but since there are long intervals between experiments for Project #1, two additional very focused projects will continue as time permits. All three projects still address the questions above. Project #2. The KISS1 metastasis suppressor gene, discovered by us, encodes a polypeptide precursor that can be processed into smaller peptides (kisspeptins) which have roles in cancer metastasis, pregnancy, and puberty. KISS1 dramatically reduces metastasis when re-expressed in animal models. While the precise molecular mechanisms governing KISS1 function are not yet known, we have observed that KISS1 renders cells that have already departed the primary tumor incapable of dividing in other tissues. This property portends well for KISS1 as a therapeutic, since most tumors have been shedding cells for many months to years by the time they are diagnosed. Recently, we have found that KISS1 controls mitochondrial reproduction. We propose to begin dissecting the mechanisms by which KISS1 regulates those processes. Project #3 explores the mechanisms underlying the function of Breast cancer metastasis suppressor 1 (BRMS1). BRMS1 is produced in a wide variety of normal human and animal tissues and the protein is typically found predominately in the nucleus where it associates with machinery that regulates gene expression. Recent data suggest an alternative mechanism of action – regulation by cellular machinery that controls cell division. We will: (1) determine BRMS1 interactors using yeast two-hybrid screening and co-immunoprecipitation; and (2) use alanine scanning site-directed mutagenesis to mutate a domain we previously identified as essential for metastasis suppression.