**Susan G. Komen for the Cure**
**Research Grants – Fiscal Year 2011**

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***Personalized Breast Cancer Vaccines Based on Genome Sequencing***

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Washington University at St. Louis, Missouri
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Research Focus: Prevention

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Public Abstract:
PUBLIC ABSTRACT The successful development of vaccines for viral disease was one of the most significant medical achievements of the twentieth century. One reason why vaccines for viral disease have been so successful is because the human immune system is programmed to discriminate between 'self' and 'non-self'. In other words the immune system is programmed to recognize and kill cells infected with a virus ('non-self'), but not normal tissues ('self'). The current paradigm in the cancer vaccine field is to target self-differentiation antigens, because self-differentiation antigens are often overexpressed in cancer. Many scientists believe that one reason why cancer vaccines have been so disappointing to date is because 'self' antigens are being targeted. Most, if not all, of the high affinity T cells capable of recognizing self-differentiation antigens are eliminated when T cells are programmed (a process known as thymic education). Targeting self-differentiation antigens is very difficult because the immune system is programmed to prevent this from happening. In this application we propose an innovative strategy to target unique tumor antigens present in breast cancer. Unique tumor antigens are the result of genetic changes present in the breast cancer, and in many ways these genetic changes represent what makes the breast cancer different from the rest of the body. Targeting unique tumor antigens for vaccine therapy has a number of conceptual advantages including: (1) Targeting unique tumor antigens is safer. Unique tumor antigens are expressed only in the tumor, decreasing the risk of autoimmunity. (2) Targeting unique tumor antigens is more effective. T cell responses to unique tumor antigens are high in affinity, and are not limited by mechanisms of self-tolerance. (3) Targeting unique tumor antigens is universally applicable in breast cancer. All intrinsic subtypes of breast cancer appear to have a remarkable number of candidate unique tumor antigens, suggesting that a personalized vaccine approach could be used for the treatment of all breast cancers, regardless of subtype. If targeting unique tumor antigens has so many compelling advantages, why hasn't it been done before? One reason is because until now, no experimental techniques have been capable of rapidly and systematically identifying unique tumor antigens. Sequencing the first human genome was an enormous undertaking, costing millions of dollars, and years to accomplish. Massively parallel DNA sequencing technologies have transformed genome sequencing, significantly decreasing the cost and time required to sequence human cancer genomes. It is estimated that the cost of sequencing a human genome will soon be less than $1,000, and may take only a few days. We are leaders in the field of cancer genomics. We were the first to sequence and comparatively analyze a tumor and normal genome from a patient with acute myeloid leukemia (Nature 2008, 456:66), and we have performed similar studies in breast cancer (Nature 2010, 464:999). In unpublished studies, we have successfully sequenced

over 50 breast cancer tumor/normal pairs. Although genome sequencing will influence breast cancer research for years to come, genome sequencing has more immediate translational implications. Identification and validation of mutations in individual breast cancers provides an unprecedented opportunity to target unique tumor antigens with personalized breast cancer vaccines. The hypothesis of this application is that unique tumor antigens can be identified by breast cancer genome sequencing, and personalized breast cancer DNA vaccines incorporating multiple unique tumor antigens can induce breast cancer immunity. In Task 1 we will generate T cell lines specific for unique tumor antigens, and determine if they can recognize and kill breast cancer cells. These proof-of-principle studies will demonstrate that genome sequencing can be used successfully to identify unique tumor antigens. These studies take advantage of our expertise in genome sequencing, and other unique resources at Washington University School of Medicine. In Task 2 we will optimize a strategy for creating personalized breast cancer DNA vaccines. These studies take advantage of our expertise in antigen processing and DNA vaccines. In Task 3 we will test personalized breast cancer vaccines in an animal model. This will provide the rationale for a phase I clinical trial. In Task 4 we will test strategies that are capable of improving DNA vaccines. These studies are focused on improving CD8 T cell memory. Our recent data suggests that failure to induce CD8 T cell memory is a significant weakness of current cancer vaccines. In Task 5 we will perform a phase I clinical trial of the personalized breast cancer DNA vaccine strategy. The main objectives of the study are to document the safety of personalized vaccines, and their ability to induce an immune response capable of killing the patient's own breast cancer cells. We are convinced that the proposed research meets the goals of the Promise Grant award mechanism. The current paradigm in tumor immunology is targeting shared tumor antigens. We propose a conceptually innovative new paradigm: development of personalized breast cancer DNA vaccines targeting unique tumor antigens identified by genome sequencing. We will initiate a phase I clinical trial of the personalized breast cancer vaccine strategy during the period of support, with the potential to directly benefit individual breast cancer patients.