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

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*Imaging Breast Cancer with Tc-99m Labeled Acridines by Targeting Telomere/Telomerase Complex*

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**Awarded:** $180,000  
**Grant Mechanism:** Post Doctoral Fellowship - Basic Research  
**Research Focus:** Early Detection

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**Public Abstract:**

**BREAST CANCER RELEVANCE:** Breast cancer is the most commonly diagnosed cancer in women and the second leading cause of deaths among women worldwide. An estimated 207,090 new cases of breast cancer will occur in the United States during 2010, 39,840 of whom will die from the disease. Metastatic breast cancer is characterized by spreading of cancer cells into nearby breast tissue, and other body parts, particularly the bone, lymph nodes, liver and lungs. The prognosis is favorable for women with clinically confined tumors at the time of diagnosis, but mortality rates are >80% in the cases where the tumor has metastasized. Thus, early detection remains the best approach for improving the odds of curing breast cancer. **NEED FOR BETTER RADIOTRACERS:** Over the last 20 years, many radiotracers have been developed by using radiolabeled receptor ligands. Without any doubt, these receptor-based target-specific radiotracers can provide a wealth of information with respect to biological changes in the tumor tissues at the molecular level. However, they all suffer a “fatal flaw” because only a small percentage of human tumors express that specific receptor. Therefore, it is highly desirable to develop a molecular probe that could detect cancers by targeting a biomarker overexpressed in majority, if not all, of human cancer tissues. Telomerase is such a biomarker overexpressed in ~90% of human breast tumors. **RATIONALE:** Telomerase is a ribonucleoprotein complex containing two components, a telomerase reverse transcriptase catalytic subunit (TERT) and a telomerase RNA template (TERC). In normal cells, progressive shortening of telomere occurs with each cell division that ultimately results in cellular senescence. Conversely, cancer cells have active telomerase that maintain the telomere length and provide those cells with unlimited cell division. Since telomerase is overexpressed in most human breast tumors (>90% of all human breast cancer tissues) but not in normal tissues, and the telomerase activity often correlates with the acquisition of a more malignant phenotype, it has been suggested that telomerase is responsible for the unchecked growth in cancer cells, and grants the cell immortality by maintaining telomere length so that the tumor cells never receive a signal to stop dividing. The telomerase is regarded as a universal “tumor antigen” and the best biomarker for breast cancer detection. **HYPOTHESIS AND OBJECTIVES:** In this project, acridines will be used to target one of the most important hallmarks of cancer: the telomere/telomerase complex (higher telomerase activity in >90% of breast cancer tissues as compared with normal cells). MAG2 will be used as the bifunctional chelator for Tc-99m-labeling. Our hypothesis is that the Tc-99m labeled acridines (G4 stabilizers) are able to selectively localize in breast tumor cells because of the low lipophilicity to limit their uptake in normal organs, the elevated negative plasma potential in tumor cells for their intracellular accumulation, and the high tumor telomerase activity for their nuclear localization. This project is specifically designed to
test this hypothesis, and evaluate Tc-99m-labeled acridines as new radiotracers for tumor imaging by single photon emission computed tomography (SPECT). The main objective is to demonstrate the proof-of-concept for the radiotracer design and to provide sufficient data for successful submission of a future NIH/DOD application. Our long-term goal is to develop a clinically useful Tc-99m radiotracer for early diagnosis in ~90% of breast cancer patients. ADVANTAGES OVER OTHER RADIOTRACERS: This project is the first to use the telomere/telomerase complex-targeted molecular imaging probes for breast cancer imaging. We believe that the 99mTc radiotracers developed in this project might become very useful for detecting the early telomerase activity changes in >90% of breast cancer patients. The key advantages of targeting the functional telomere/telomerase complex over other cancer targets (receptors or antigens) are its relative universality, criticality and specificity of telomerase activity in cancer cells. Successful development of such an imaging probe will help physicians to detect the location of tumor(s) and to select the appropriate patients for a specific therapeutic regimen based on the size and location of tumor mass. For example, the surgeons could remove the lump if the telomerase activity in a breast tumor is low. If the higher level of telomerase activity is detected in the breast tumor, the patient might respond better to a mastectomy and chemotherapy.

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