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

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***The Use of 2ME2 as a Novel and Effective Therapy for the Treatment of Endocrine Resistant Breast Cancer Growth, Metastasis and Tumor-induced Bone Osteolysis***

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Awarded: $450,000.00
Grant Mechanism: Career Catalyst Research
Research Focus: Treatment

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Public Abstract:
Breast cancer is the second leading cause of cancer related deaths in the United States and affects approximately 1.3 million women worldwide each year. Of these individuals, two-thirds will have tumors that are considered to be endocrine responsive based on expression of the estrogen receptor (ER). ER positive patients are commonly treated with tamoxifen, the most important present day drug for the management of breast cancer, to inhibit the proliferation inducing effects of estrogen and slow the progression of their disease. Despite the tremendous advantages of tamoxifen in the treatment of women with hormone sensitive cancers, a significant proportion of these individuals will experience disease progression due to the development of resistance to endocrine agents. The development of endocrine resistance represents one of the most troublesome clinical issues today as there are no specific therapies to treat patients with such disease. Indeed, a devastating reality of endocrine resistant breast cancer is its association with incurable metastatic disease. Nearly 40,000 women die each year as a result of breast cancer metastasis and nearly 60% of these women die within 5 years of their diagnosis. Of all breast cancer metastatic sites, the spine, ribs, pelvis, and proximal long bones are the most common, leading to debilitating skeletal complications such as bone loss, intractable bone pain, and pathologic fractures. While several new therapies, such as bisphosphonates, are somewhat effective in suppressing tumor-induced bone loss, they do not slow the progression of the tumor itself which ultimately continues to proliferate and metastasize to other organ sites. Therefore, these therapies are not of significant benefit to the overall health of the patient and do little to extend their lifespan. As a result, chemotherapy and radiation therapy are commonly employed to treat endocrine resistant and metastatic tumors. Unfortunately, these drugs and treatment strategies have severe side effects which negatively impact a patient's quality of life and only slightly improve long term survival rates. Clearly, alternative therapies with fewer side effects are drastically needed for the treatment of endocrine resistant tumors, metastatic breast cancer and debilitating bone loss as a result of tumor-induced osteolysis. 2-methoxyestradiol (2ME2), a naturally occurring metabolite of estrogen produced in the body, has recently shown significant promise as such a drug as it induces tumor cell apoptosis both in vitro and in vivo without affecting normal cells. Our preliminary studies have shown that 2ME2 is very effective in targeting and eliminating multiple types of breast cancer, including endocrine resistant tumor cells. Additionally, we have demonstrated that 2ME2 is highly effective at blocking the formation of osteoclasts, the cell type responsible for tumor-induced bone loss. These data strongly suggest that 2ME2 could be a universal therapy that would suppress and/or prevent breast cancer

tumor growth, metastasis and tumor-induced bone loss. While our research, as well as that of others, has demonstrated significant promise for the use of this drug in treating multiple types of cancer, significant limitations existed due to poor bioavailability of 2ME2 when administered orally. This limitation has recently been overcome through the formulation of an orally-administered liquid suspension (Panzem® NCD) developed by ENTREMED Inc., which exhibits 5-10 fold increased bioavailability and results in circulating concentrations of 2ME2 that are known to exhibit optimum anti-tumor activity in preclinical studies. To date, no one has examined the efficacy of Panzem (2ME2) in the treatment of endocrine resistant disease. Therefore this proposal will be the first to investigate the effectiveness of this drug as a novel therapeutic to treat, reverse and prevent endocrine resistant breast cancer growth, as well as its associated metastasis and osteolytic bone damage. The completion of the proposed studies will significantly enhance our knowledge regarding the actions of 2ME2 and will identify the effectiveness of Panzem® NCD as an alternative therapy for patients whose tumors have developed endocrine resistance. Finally, successful completion of these studies will implicate 2ME2 as the first drug to universally treat multiple forms of resistant and metastatic breast cancer, as well as its associated bone damage, and will lay the groundwork for developing informed clinical trials to further test this possibility in patients. The eventual use of this drug in the clinical setting has the potential to rapidly enhance the quality of life and extend the lives of thousands of women around the world each year.

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