



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

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Mechanisms of Endocrine Action: ER-Induced Apoptosis and HRT-associated breast cancer

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Lead Organization: UT M.D. Anderson Cancer Center

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Public Abstract:

There is currently an enormous amount of interest in the new biology of physiological estrogen action since the publication of the results of the Women's Health Initiative (WHI) Trial of the impact of long term conjugated equine estrogen (CEE) alone as hormone replacement therapy for hysterectomized postmenopausal women (Anderson et al, Lancet Oncol 2012; 13:476-486). Remarkably, there was a significant decrease in the incidence of invasive breast cancer and this decrease was maintained for five years after stopping CEE treatment. These paradoxical clinical results have now opened a window of opportunity by using laboratory models to discover and amplify the mechanisms of estrogen-induced apoptosis to aid more women to either prevent breast cancer or to control breast cancer growth following the failure of conventional therapies. The results of the WHI are consistent with an emerging body of laboratory evidence that is currently deciphering the molecular mechanism of estrogen-induced apoptosis and applying this knowledge to the treatment of breast cancer following the failure of multiple antihormone therapies (tamoxifen or the aromatase inhibitors). This evidence has recently been summarized (Jordan and Ford, Cancer Prevention Research 2011; 4:633-637) and our current project is focused entirely on discovering the molecular mechanism of estrogen-induced apoptosis in our laboratory model systems with the ultimate goal of enhancing tumor responsiveness under the correct environmental conditions from about 30% to 50% and above. It is our intention through the study of molecular mechanisms in the laboratory, to amplify breast cancer responsiveness to physiological estrogen to trigger apoptosis and aid increased survivorship from breast cancer. Indeed, if we can discover the molecular mechanism whereby estrogen triggers apoptosis through the breast cancer cell estrogen receptor (ER), we may in fact be able to use the cellular target for a new drug discovery program to induce cancer cell death with an entirely new group of medicines.