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

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Targeting stem and myoepithelial cells with nutritional compounds to prevent breast cancer in women with high risk ductal carcinoma in situ

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

Public Abstract:
I propose that using nutritional compounds to decrease breast stem cell ability to make more stem cells (self renewal)and promotion of differentiation into myoepithelial cells, which surround the breast ducts to prevent invasion of cancer cells can reduce risk of invasive breast cancer and recurrent ductal carcinoma in situ in women at high risk. Curcumin and piperine are two nontoxic nutritional spice isolate compounds with the potential to modulate Wnt, Notch and Hedgehog, the signaling pathways in cancer cells which control stem cell expansion and myoepithelial cell differentiation. Changes in stem cell number and signaling inside stem cells could serve as novel molecular targets for curcumin and piperine to reduce risk of invasive ductal breast cancer and recurrent DCIS in women with high risk DCIS. I have previously shown that curcumin and piperine, two nontoxic nutritional spice isolate compounds, independently decreased normal and breast cancer stem cell self renewal (40). For the purposes of invasive breast cancer risk reduction we need to specifically test if these compounds can reverse or prevent the events of invasive carcinogenesis in women at high risk. Therefore, I propose to address the following Objectives: Objective 1 is to examine the effect of curcumin, piperine and the combination of agents at various concentrations on DCIS stem/progenitor and myoepithelial cells isolated freshly from human DCIS mastectomy tissue and from two DCIS cell lines MCF10DCIS.com (basal) and SUM 225 (Her2Neu overexpressing) in vitro, including a) DCIS stem cell self renewal, and number, b) myoepithelial cell number, and c) Wnt, Notch and Hedgehog signaling. I recognize that in vitro examination of fresh human explant cells does not replicate in vivo biology fully, however, it allows testing of human cellular signaling and function in carcinogenesis more closely than use of cancer cell lines. I specifically chose the MCF10DCIS.com and SUM 225 DCIS cell lines because they are estrogen receptor negative and represent the aggressive biology of basal DCIS and Her2Neu overexpressing DCIS respectively, neither of which can be prevented with tamoxifen or raloxifene. The in vitro studies allow examination of mechanism of activity and potential efficacy of the proposed nutritional intervention agents. I have already published a similar set of work with curcumin and piperine targeting normal (from fresh human breast tissue explants from reduction mammoplasty surgeries) and malignant breast stem cells (from cancer cell lines) to decrease self renewal under the mentorship of Drs. Wicha and Brenner (1). There are no rodent models of breast stem cell biology and cancer risk reduction intervention testing which can truly replicate human biology. The commonly used immunosuppressed rodents have immature gut systems which do not metabolize or handle oral administration of nutritional interventions similarly to humans. Transgenic and chemical carcinogen rodent models also do not replicate human biology. Thus,

data from rodent models is of limited application to understanding human biology. In response to reviewer concern about over ambitious scope of the my pre-application I have removed resveratrol and the proposed Phase 1 study from this full application. With Dr. Dean Brenner's mentorship in prevention clinical trial design, implementation and analysis, I have received funding for a dose escalation human Phase 1 study of curcumin and piperine from the NCI K07 mechanism. This Phase 1 study will be completed in 18 months (by the time the pilot feasibility study in this proposal is planned). Both curcumin and piperine are nutritional isolates which have been tested in multiple human clinical trials and shown to be nontoxic. Therefore, we can proceed directly to human testing rather than the limited rodent models. Objective 2 is to conduct a Pilot randomized presurgical feasibility study in 20 women with high risk DCIS going for mastectomy randomized to 28 days of oral dosing with curcumin and piperine and 20 women to placebo to determine: a) breast tissue concentrations of the intervention agents. Objective 3 will test feasibility of identifying changes in breast stem and myoepithelial cell number and Wnt, Notch and Hedgehog signaling as biomarkers of breast cancer risk reductive intervention efficacy. These objectives will provide preliminary data to determine if we can successfully deliver bioactive concentrations of curcumin or piperine to human breast tissue. The pilot study will also provide preliminary data on whether human breast stem/progenitor cells may serve as novel molecular targets and potential biomarkers of breast cancer risk reductive agent (chemopreventive agent) efficacy. The data from these studies will support an independent research grant application to test these agents in a sufficiently powered Phase 2a proof of principle study in patients with high risk estrogen receptor (ER) negative as well as ER positive DCIS (as defined by Van Nuys index greater than 9). The specific targeting of human DCIS stem cells, use of stem and myoepithelial cells as biomarkers of efficacy and combination of nutritional isolates for synergy of mechanism and enhanced bioavailability are all innovative strategies applicable to invasive breast cancer prevention today. Komen Foundation Career Catalyst Funding would provide me with valuable resources to generate the preliminary data to substantiate future independent peer reviewed funding applications as well as provide me with continued mentorship to help me transition to independence in the field of translational cancer risk reduction research.