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

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Rational Molecular Multi-targeting in High-risk Breast Cancer

Investigator(s): Kevin Kozak, MD, PhD
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Awarded**:** $450,000.00
Grant Mechanism: Career Catalyst Research
Research Focus: Treatment

Public Abstract:
Breast cancer is the single biggest cancer killer in women accounting for 14% of all female cancer deaths worldwide. Metastatic cancer is by far the most common cause of death in the 410,000 women who succumb to the disease each year. Despite great strides in treatment over the past several decades, current standards of care afford unacceptably poor outcomes in patients with metastatic disease, particularly those with tumors unresponsive to hormonal therapies. Consequently, substantial progress in breast cancer management can be achieved through improvements in our ability to prevent and treat hormone-refractory metastatic disease. To advance metastatic disease prevention and treatment, more active and better-tolerated therapies are needed. Since President Nixon's 1971 declaration of "War on Cancer," two frustrating themes in breast cancer research have emerged. First, the enemy is resilient. Despite the application of toxic agents that drive patients to the brink, metastatic breast cancer universally prevails. Cancer cells are remarkably adept at persisting despite prolonged, sequential exposure to highly toxic therapies. Second, the enemy is clever. Volumes of basic molecular information have been compiled leading to the recognition that cancer cells do not develop and grow through the alteration of individual signaling pathways. Rather, cancer cells orchestrate a wide range of alterations that promote relentless growth. Even when one important signaling pathway is completely blocked by a drug, cancer cells can engage alternative or compensatory pathways to overcome the block. How then do we make serious inroads in this fight? We believe that simultaneous targeting of multiple important pathways offers real promise. Through the shrewd selection of targets, resilient cancer cells may be overwhelmed. Moreover, the alternative pro-survival pathways cleverly engaged by cancer cells exposed to toxic therapy can be inhibited from the start. Unfortunately, the apparently straightforward task of simultaneously targeting multiple critical pathways is enormously challenging; not only do the right drugs need to be identified, they must be delivered in a tolerable and complementary way. We have identified multiple key pathways implicated in high-risk breast cancer progression and therapy resistance. More importantly, we have identified a combination of three drugs that potently inhibits these pathways. To test our hypothesis that simultaneous targeting of multiple signaling pathways has considerable promise in high-risk breast cancer, we have proposed to advance this drug combination from basic cellular studies to classical tumor studies in mice and, finally, to advanced models of metastatic disease prevention and treatment. To facilitate transition from cellular studies to animal studies (and human clinical trials), we exploit a novel nanoparticle that permits simultaneous encapsulation and safe delivery of the three-drug combination. This advance, developed by our multidisciplinary team, overcomes a host of logistical and pharmaceutical obstacles. We believe this

novel drug delivery system is critical to the success of our multi-targeted approach to breast cancer treatment. Early preclinical studies provide great cause for optimism. We have shown the three-drug combination is remarkably efficiently encapsulated by our selected nanoparticle. Furthermore, early studies suggest that the combination's anti-cancer activity is "greater than the sum of its parts" lending credence to the hypothesis that simultaneous targeting of multiple pathways will be more effective than either traditional single pathway targeting or sequential targeting of multiple pathways. Finally, preliminary experiments in mouse models of high-risk breast cancer document unprecedented anti-tumor efficacy. Although these results represent the earliest steps on the path to clinical benefit, they strongly support continued evaluation of the multi-targeting strategy. Success in the laboratory does not guarantee success in the clinic. In anticipation of this exceedingly challenging transition, we have selected drugs that have previously been examined in human studies and shown to be safe. Moreover, the nanoparticle used in the proposed research has been tested in humans. Not only has this nanoparticle been shown to be an efficient drug delivery vehicle, early human trials have demonstrated that it reduces the side effects commonly associated with drug vehicles. These clinical observations should allow promising findings to be rapidly translated into clinical trials. Our team has already established an aggressive timeline for transition to clinical testing and has engaged key institutional resources to ensure this becomes a reality. Finally, our team and panel of expert advisors possess a broad range of scientific and clinical expertise allowing us to transform unforeseen preclinical findings into novel opportunities. Consequently, we believe the proposed research has real potential to quickly and positively impact patients with breast cancer.