Susan G. Komen

Research Grants – Fiscal Year 2015

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Chromosomal enhancer/architectural misregulation in breast cancer

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Public Abstract:

Of the 180,000 cases of invasive breast cancer diagnosed each year in the United States, more than 70% express estrogen receptor a (ERa), and are subjected to endocrine therapies. However, approximately 30% of ERa-positive (ER+) breast cancers exhibit de novo resistance, whereas 40% acquire resistance to these therapies. Endocrine-resistant ER+ disease accounts for approximately one in four breast cancers, similarly to the triple-negative phenotype that does not express ERa, progeesterone receptor (PR) nor ERBB2 amplification, and it is not well served by current targeted therapies. Two major challenges for the successful treatment of breast cancer are the development of more specific biomarkers that predict therapeutic response to endocrine therapies and the identification of new therapeutic targets for endocrine-resistant disease. A prerequisite towards this goal would be a better understanding of ERa-mediated transcriptional network, exhibiting estrogen-dependent activation in the initial but later developing ligand-independent “autonomy” during cancer progression and/or following endocrine therapies. Recently, genomic sequencing of ER+ breast tumors before and after hormone deprivation revealed condensed recurrent mutations in ESR1, a gene coding for ERa. Of note, mutations in ESR1 are rare in treatment-naive primary ER+ breast cancer samples, indicating that ESR1 mutants are selected by hormone deprivation therapy, possibly as a result of the reduced estrogen state caused by aromatase inhibitors. However, the mechanistic nature of these selected ERa mutants, specifically their genome-wide transcriptional targets and the key underlying molecular events required for ligand-independent transcription activation, remains poorly understood. As advanced technologies have begun to uncover

previously-unknown aspects of ERa- and/or the hormone-refractory mutant ERa-mediated transcriptional networks at the full chromosomal level, it is now, for the first time, possible to link the emerging discoveries, from clinical and basic research, to the mechanisms of ERa regulatory transcriptional programs important in breast cancer etiology. This proposed study will begin to address this important question and provide critical insights into the regulation of ERa-mediated gene transcriptional programs. This will uncover novel and previously-unsuspected key steps in ERa regulation of gene transcription that are likely to serve as new, potential targetable candidates for ER+ breast cancer patients who are refractory to hormone therapies. This proposed research would significantly advance our understanding of how ERa mutants succeed in evading hormone deprivation to activate cancer gene transcriptional programs, and will also facilitate the translation from bench to bedside by examining a novel combination strategy that would likely achieve a synergistic antitumor effect by simultaneously targeting estrogen/ERa and its regulatory programs required for the breast cancer progression.