Susan G. Komen for the Cure
Research Grants – Fiscal Year 2012

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The Potential Role of TLK2 as a Therapeutic Target in Breast Cancer
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Awarded: $180,000.00
Grant Mechanism: Postdoctoral Fellowship

Public Abstract:
Increased genomic instability and the accumulation of numerous chromosomal aberrations are hallmark characteristics of advanced breast cancer, which is particularly prominent in late stage tumors. Studying driver chromosomal aberrations on key kinases in the DNA damage pathway may shed light on the origin of the genomic instability, and targeting their activity could offer a new and valuable treatment option for tumors harboring these gene derangements. This could be particularly valuable in the management of late stage advanced breast tumors. In our lab, we have systematically nominated tousled-like kinase 2 (TLK2) as a candidate therapeutic target from 44,932 human genes using bioinformatics workflows based on genomics datasets from The Cancer Genome Atlas. TLK2 is a nuclear serine/threonine kinase which is a cell cycle checkpoint regulating chromatin assembly, and is inactivated in response to DNA damage. Interestingly, in invasive breast cancers, we observed a 10-12% prevalence of focal gene amplifications and 2% incidence of gene translocations at the TLK2 locus. TLK2 amplifications are more frequent in Luminal B subtype, a high-grade breast cancer prone to early and frequent recurrence and metastasis. Furthermore, we observed increased genomic instability in breast tumors over-expressing TLK2; whereas p53 missense mutations are less frequent in these tumors. We hypothesized that deregulated TLK2 kinase activity may push the cells to escape the cell cycle checkpoint upon DNA damage in breast cancer, thus destabilizing the cancer genome. This is supported by our preliminary data showing that TLK2 transient knockdown substantially inhibits breast cancer cell proliferation in TLK2 over-expressing breast cell lines. This inhibitory effect is sustained even in their derivative strains resistant to tamoxifen or anti-Her therapies. In this Komen project, I propose to investigate the potential role of TLK2 as an attractive therapeutic target in the management of advanced breast cancer. I will examine the role of TLK2 deregulation in breast tumorigenesis, cellular escape from DNA damage checkpoint and increased genomic instability, through inducible knockdown and over-expression of TLK2 in vitro. Then the clinical relevance of TLK2 derangements will be elucidated by fluorescence in situ hybridization and immunohistochemistry studies of breast cancer tissues microarrays. The role of TLK2 in breast tumor formation will be investigated using in vivo xenograft mouse models, and the potential clinical implications of TLK2 inhibition as sensitizing agent to therapeutic resistance will be explored. Overall, I expect that this study will provide compelling evidence regarding the role of TLK2 in breast cancer tumorigenesis and genomic instability, and establish its potential as a therapeutic target.