Targeting the cell cycle in sporadic & BRCA mutant triple negative breast cancer

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Grant Mechanism: PDF Basic and Translational

Public Abstract:

Through the investigation of this proposal we seek to 1) understand BRCA1 mutant breast cancer development through deregulation of the cell cycle and 2) investigate novel treatment therapy for Triple Negative Breast Cancer (TNBC). Through the help of my mentor Dr. Khandan Keyomarsi and advisory committee of physicians & research scientist, we will seek to investigate research directives with immediate clinical impact. Our laboratory focuses on the essential role of cell cycle deregulation in breast cancer progression. Our research has highlighted the essential functions of Low Molecular Weight isoforms of cyclin E (LMW-E) in transforming the tumor microenvironment and promoting resistance and relapse in breast cancer patients. This research will serve as the fundamental cornerstone of understanding BRCA mutant breast cancer progression, the most significant indicator of breast cancer risk. Germ-line mutations within BRCA1/2 are the strongest predictors of life time risk of developing breast cancer, however not a lot is known as to why some women with BRCA mutations develop breast/ovarian cancer while others do not. The cell cycle plays a fundamental role in preventing cancer cells from growing, and loss of cell cycle control is usually one of the first events to signal further breast cancer development. Therefore, we believe that loss of cell cycle control via expression of the LMW-E isoforms may be the mitigating factor in BRCA mutant breast cancer progression. Furthermore, previous research has suggested that inhibiting the activity of these LMW-E isoforms can prevent the development of breast cancer altogether in genetic mouse models. Therefore, we are seeking to not only understand the influential role these LMW-E isoforms play in breast cancer, but attempt to inhibit their activity through drugs designed to target cell cycle activity (CDK inhibitors; Dinaciclib). If we are successful in preventing the progression of BRCA1 mutant breast cancer in this genetic mouse model, then we may be able to develop prevention strategies for women with inherited BRCA1 mutations that lower the 45-65% lifetime risk. The final aspect of this research proposal seeks to provide novel therapeutic treatments for TNBC through dual inhibition of CDK activity and PARP enzymatic activity. Although TNBC patients typically respond to chemotherapy, patients often relapse shortly after treatment. PARP inhibitors are a novel class of targeted therapy that works best in patients with BRCA1 mutant tumors, with lower associated toxicities. However, BRCA mutant patients are only 20% of all breast cancers, therefore research is currently underway to make non-BRCA mutant tumors susceptible to Parp inhibitors though combination therapy. CDK inhibition mimics BRCA1 mutations making non-BRCA mutant tumors susceptible to Parp inhibition. This aspect of the research proposal seeks to lower relapse rates and increase overall survival in TNBC breast cancer patients.