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**Preclinical Development of a PEA-15-Based Therapy for Triple-Negative Breast Cancer**

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**Grant Mechanism:** Post Doctoral Fellowship - Translational Research  
**Research Focus:** Treatment

**Public Abstract:**

Background: Breast cancer is the most common cancer in the world and the second leading cause of cancer death among women in the United States. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that accounts for about 15% of breast cancers. This type of breast cancer is called “triple-negative” because the breast cancer cells do not have estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) on their surface. Since most standard treatments for breast cancer are for breast cancer cells that have ER, PR, or HER2 on their surface, patients with TNBC have fewer treatment options than patients with other kinds of breast cancer. At present, there are no FDA-approved targeted therapies available for TNBC; chemotherapy is the only systemic treatment option for patients with TNBC. Phosphoprotein enriched in astrocytes-15 kDa (PEA-15), an antitumor protein, has been shown to have tumor suppressor properties in breast cancer cells. PEA-15 can induce TNBC cell death, and treatment with PEA-15 led to shrinkage of TNBC tumors in mice. The antitumor activity of PEA-15 is related to functional inhibition of a signaling molecule called extracellular signal-regulated kinase (ERK), which is involved in cancer cell growth and differentiation. PEA-15 inhibits cell growth by interacting with ERK in the cytoplasm of cancer cells and preventing ERK from moving into the nucleus, where ERK stimulates production of many proteins essential for cell growth. Elevated ERK activity is associated with shorter survival of patients with breast cancer. Thus, ERK is an excellent target for TNBC therapy. In this proposed project, we plan to develop novel PEA-15-based peptide (protein fragment) drugs to suppress growth and spread of TNBC cells by inhibiting ERK activity.  

Hypothesis/Objective/Study Design: The overall objective of this proposal is to develop PEA-15-based peptide drugs for TNBC. The central hypothesis of the proposed project is that suppressing ERK activity by blocking ERK nuclear translocation using PEA-15-based peptide drugs inhibits growth and spread of TNBC cells. To test our hypothesis, we will carry out the following studies. First, we will synthesize a number of PEA-15-based peptides and then select at least 2 of the most potent PEA-15-based drug candidates in terms of TNBC cell killing. Second, we will investigate the antitumor mechanisms of the selected PEA-15-based drug candidates. This study will uncover how these drug candidates kill TNBC cells and identify the important molecules involved in TNBC cell killing mediated by these drug candidates. Third, we will evaluate the overall therapeutic efficacy and safety of the selected PEA-15-based drug candidates using a TNBC mouse model. Therapeutic efficacy will be evaluated on the basis of tumor size and mouse survival rate, whereas safety will be assessed on the basis of signs of toxicity and chemistry analyses of blood and tissue sections following treatment with the drug candidates. We expect that these drug candidates will effectively kill TNBC cells, reduce tumor size, and
prolong mouse survival with no or tolerable toxic effects to normal tissues. Significance: In this proposed research, we plan to develop a new peptide drug, with a structure very similar to that of PEA-15, to inhibit ERK activity. We expect that the PEA-15-based drug candidates will mimic the antitumor action of PEA-15 and be able to inhibit the growth and spread of TNBC cells. If this proposed research is successful, it will confirm our previous finding that PEA-15 inhibits the growth and spread of breast cancer cells by modulating ERK activity. This study will also advance our understanding of how the PEA-15-based drug candidates kill TNBC cells. More importantly, the success of this proposed work will lead to development of a novel PEA-15-based drug in the near future with the potential to reduce the mortality or at least prolong the survival of patients with TNBC. The knowledge and technologies applied in this proposal can be employed for the development of novel drugs that target other key signaling molecules for the treatment of different types of breast cancer. Impact on Patients: Currently, there are no FDA-approved targeted therapies for patients with TNBC. Our preliminary data have demonstrated the therapeutic potential of the PEA-15-based therapeutic approach. If this proposed project is successful, it will serve as the foundation for initiating a clinical trial to test the therapeutic efficacy and safety of a PEA-15-based drug candidate in patients with TNBC within the next 4 to 7 years. Thus, the proposed research is highly relevant to improving the outcomes of patients with TNBC, who currently have limited treatment options. This study will also significantly advance the development of targeted therapies for different types of breast cancer.