

PUBLIC/LAY ABSTRACT

Breast cancer is a big health problem mainly in women, among which triple negative breast cancer (TNBC) is the leading cause for its mortality. Approximately 15% of patients with breast cancer often develop brain metastases. Therefore, tumor progression and invasion in the central nervous system (CNS) is a major threat to patient survival. The median survival rate is less than 3 years for the patients with brain metastasis; whereas TNBC patients suffered from brain metastasis have a median survival of about 1.15 years. Currently, the treatments for breast cancer metastasis (BCM) are only limited to surgery or radiation. In particular, advanced breast cancer (such as TNBC) is very much resistant to conventional treatments. Thus, there is an urgent need for developing new therapeutics for TNBC or metastatic breast cancer.

Current strategies in drug research for developing new anti-cancer treatments have not only been focusing on finding novel chemotherapeutic compounds, but also on identifying drugs that are approved by the FDA or in clinical trials and however, can be "*repositioned or repurposed*" to treat different types of tumors or diseases. The so-called drug "repurposing" is the fastest way with the least resistance for discovering novel, effective therapies, because data for toxicology and human toxicity which are costly-expensive to generate and time-consuming are already available for such "repurposing" drugs.

In breast cancer, the α sub-form of protein kinase C (PKC α) is frequently overexpressed, increasing levels of which are correlated with enhancing malignant degrees. Therefore, we conducted the preliminary experiments to test if PKC α could be targeted for attenuating breast cancer progression. We screened a panel of PKC inhibitor-based drugs and identified several potent ones that have anti-breast cancer property. Among these drugs, bryostatin-1 (bryo1, a PKC α inhibitor-based drug, is in clinical trials for treating advanced colon cancer or leukemia) was scored the best and could specifically eliminate or kill metastatic MDA-MB-231 cells. Bryo-1 treatment also attenuated the invasive capability of TNBC MDA-MB-231 cells. Using xenograft assay, we further demonstrated that bryo-1 injection suppressed the brain metastasis of the implanted TNBC BrM2/*GFP* tumors in the nude mice. Based on our preliminary data, we hypothesize that bryo-1 is able to be repurposed for treating metastatic breast cancer or TNBC. This drug, via inhibiting PKC α , induces ROS and upregulates adherent molecules, leading to effectively block breast cancer progression and metastasis.

The goal of our proposed study is aimed to addressing how bryo1 induces oxidative stress for increasing the vulnerability of metastatic breast cancer/TNBC cells and if the drug attenuates breast tumor cell invasion or further brain metastasis. Our proposal is of high significance with clinic translation, because bryo1 is already in clinical studies for treating other types of human diseases, and all the data from time-consuming/expensive toxicology studies as well as from clinical evaluations to prove human tolerance for this drug are already available. We expect that the outcomes of our proposal will help quickly move bryo1 to clinical studies for treating metastatic breast cancer and TNBC.

In summary, our proposal has the potential for developing novel therapeutic targets as well as targeted therapeutic strategies to treat this devastating disease that mainly occurs in women. Thus, our application is in the full accordance with the mission of METAvivor Foundation. Furthermore, with the help of METAvivor funding, our proposed research will be expedited for clinic implement of bryo1 in the near future to help patients with the stage IV of breast malignancy living in better or manageable conditions.