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 10% to 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.

To date, the essential tasks for researchers are to identify new molecular targets and consequently develop potential targeted, therapeutic strategies for BCM treatments. Therefore, obtaining better understanding of the mechanisms by which breast cancer cells metastasize to the brain becomes the first, important step for developing innovative treatments with high efficacies.

We have shown that during the process of breast malignant transformation, changes of metabolic pathways (such as those regulating glycolysis and lipids) occurred. Furthermore, monoacylglycerol lipase (MGL) played an important role in regulating lipid signaling in pre- and breast cancerous cells, but not in normal cells. Based on these findings, we in this application will elucidate the mechanisms by which MGL, via altering lipid metabolisms, promotes breast tumorigenesis and further TNBC metastasis.

The goal of our proposed study is aimed to addressing how MGL aberrantly upregulates the fatty acid signaling network in breast cancer/TNBC cells and if the suppression of MGL by our newly synthesized MGL inhibitors can block or attenuate breast tumorigenesis or metastasis. Our proposal is of high significance with clinic translation, because MGL inhibitor-based drugs are 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 potent drugs with MGL inhibitory nature are already available. In this application, we will investigate two highly potent MGL inhibitors AM4301 and AM9928 that are synthesized and characterized by the scientists in our department and us in the collaboration form. If outcomes of this research demonstrate the potential of these two MGL inhibitory compounds in effectively eliminating advanced breast cancer cells or attenuating their progression with sustainable pharmacodynamics, we expect that these inhibitors can be quickly moved to clinical studies.

Our preliminary data showed that MGL inhibition played an important role in blocking TNBC-associated inflammation and tumorigenesis. In this application, we will use several mouse models to examine the role of MGL in regulating lipid metabolism in tumor cells and its inhibition in blocking tumor growth and brain metastasis. We will also study the role of MGL in its junction dynamics during the trans-endothelial migration of breast cancer cells across the blood brain barrier (BBB) and test the ability of the MGL inhibitors in preventing tight junction degradation for restoring the integrity of the BBB. Our study may prove that targeting this lipid pathway is a novel approach for developing effective breast cancer therapeutics.

In summary, dysregulation of lipid networks represents an important aspect of breast cancer progression and metastatic colonization. Optimal treatment and anti-metastatic drugs should come from inhibiting breast cancer colonization, growth and metastases. By focusing on TNBC and metastatic TNBC, our proposal has the potential for developing novel targeted therapeutic strategies to treat this devastating disease mainly in women, which is in the full accordance with the mission of METAvivor Foundation. Furthermore, with the help of METAvivor funding, our proposed research will be expedited and these MGL inhibitors/drugs can be implemented clinically in the near future to help patients with the stage IV of the malignancy living in a better or tolerable condition.