***Public/Lay Abstract***

Approximately 40,000 patients die from breast cancer every year in the US. More than 90% of the deaths are attributed to metastatic disease, and the brain is one of most common metastatic sites of breast cancer. Brain metastasis (BrM) is almost always fatal with an average survival period of 2.3 months. Treatment options for patients with BrM are quite limited, mainly due to the inability of current drugs to penetrate the blood–brain barrier (BBB). Many patients experience a relapse in the form of local and distant metastatic disease, possibly due to tumor cells that resistant to the treatments and the unique brain microenvironment that protects them from various anti-cancer therapies. Therefore, a better understanding of the features of brain metastatic cells and the microenvironment support their growth is urgently needed to develop novel therapeutic approaches to this devastating disease. A significant decreasing of BrM burden was reported in clinical trials among lung cancer and melanoma patients who received the immune check point inhibitor (CPI), indicating that CPI may be effective to breast cancer patients with BrM. Notably, the efficacy of CPI depends on many factors such as the mutation burden, PD-L1 expression and the amount of immune suppressor cells in the tumor area. Furthermore, the presence or absence of primary tumor also play a critical role in the CPI response of metastatic tumors. We found that the response rate to CPI in breast cancer BrM patients is determined by the level of c-Met expression in tumor cells. High level of c-Met will generate an immune suppressive brain microenvironment which impairs the efficacy of CPI by promoting the phenotype switch of microglia cells from tumor suppressive (M1) to tumor promoting (M2). We previously identified pterostilbene (PTER) as a BBB permeable natural compound that suppresses BrM by specifically blocking c-Met expression. We believe that stage IV breast cancer patients who still have the presence of primary tumor either have been diagnosed with BrM or have disseminated tumor cells in the brain which are not fully grown yet will be beneficial to the CPI and PTER combination therapy. Our ultimate goal is to eliminate detectable BrM as well as disseminated tumor cells that responsible for the future brain relapse. As a first step to achieve this goal, we will design experiments to examine the molecular mechanisms of how c-Met induced TGF$\beta$ facilitates the phenotype switch of microglia(M1 to M2) and whether M2 microglia attenuate the efficacy of CPI by suppressing T cells in the brain (Aim1). We will also test the efficacy of combination therapy of CPI and PTER in our unique syngeneic BrM models and BrM PDX models in humanized mice (Aim 2).