**Lay Summary**

Rationale and Objective

TNBC is one of the most deadly diseases, with unmanageable symptoms. This metastatic breast tumors can’t be treated with hormonal therapies or HER2-targeting medicines that are used for some other types of breast cancer. Therefore, the prognosis of TNBC is very poor, and the recurrence rates are relatively high. Current chemotherapeuric regimens are often ineffective, and also associated with significant toxicity that can severely reduce quality of patient’s life. Therefore, it is very important or urgent for medical researchers to discover promising drugs that can be rapidly moved into clinical trials for reducing suffers of TNBC patients.

Ultimate Applicability of the Research

Highly potent carbamate MGL inhibitor-based compounds A4300 and A9920 were synthesized and characterized by the chemistry team of our research center. The preliminary studies demonstrate that these two MGL inhibitor-based compounds are able to target fatty acid synthesis with very little side effects. In the first funding year, we established faithful PDX mouse models of TNBC, by implanting the patient bresst tumor cells into NOG mice. To test new compounds that inhibit lipid synthesis pathways essential for NTBC cell growth and survival, we isolated TNBC cells from primary PDX tumors and grow them in cell culture plates, which renders the easy way to test the MGL inhibitor or newly synthesized MGL inhibitor-based compounds in a relatively short amount of time. Furthermore, we characterized these cultured cells with the emphasis on tumor structure, growth pattern and tumor marker expressions. We also established the MGL overexpression or knockdown transfectants from these isolated breast tumor cells. In addition, we have been analyzing the inhibitor or compounds for their ability to antagonize the growth of TNBC cells in our experimental settings. We are in the process to test if these compounds are able to block TNBC cell invasion and brain metastasis.

Advancement of TNBC research and Patient Care

We predict that the experiments proposed in this application will likely prove that our newly synthesized MGL inhibitor-based compounds possess the properties of antagonizing the growth and metastasis of TNBCs. Our on-going study is relatively novel, because we are screening and identifying the high efficacies of our new MGL inhibitor-based compounds in treating TNBCs. We also established TNBC patient-derived cell lines in regular tissue culture system, which allows producing and evaluating results in a fast pace. With these useful tools in our hands, promising compounds can be tested by the in vitro and in vivo experiments. We expect that outcomes of our study will further promote clinical trials of our new MGL inhibitor-based compounds, which may lead to discover new drugs that can improve living conditions of TNBC patients.