Public Abstract

Breast cancer is the most common malignancy of women. Among the breast cancer varieties, or subtypes, triple negative breast cancer (TNBC) makes up to 15-24% of all breast cancers. TNBC is a highly aggressive disease with a poor outlook, a high rate of tumor return despite treatment, and is linked with the shortest overall survival. Compared to other breast cancer subtypes, the rates of brain metastasis occur more frequently for TNBC, where advanced TNBC constitutes approximately 46% of brain metastases. Standard treatment for patients with brain metastatic TNBC (TNBC-BM) consists of surgery followed by whole brain or precise high-powered non-surgical radiation treatment. Despite heavy investment in new therapies, median survival of patients with TNBC-BM is only 4.9 months. Since no FDA approved treatments for TNBC-BM exist, there is an urgent need for new therapies to treat TNBC-BM.

Although changes to DNA in the form of alterations to important genes such as BRCA1/2 have been linked with breast cancer, reversible changes to molecules that closely associate to DNA can change gene expression that may contribute to cancer. These reversible changes, known as epigenetic alterations, have been shown to play a pivotal role in TNBC-BM development and disease progression. The enzyme lysine-specific histone demethylase 1A (KDM1A) plays a part in promoting these epigenetic alterations. Importantly, KDM1A is highly expressed in TNBC and is associated with worse survival. Additionally, oxygen deficiency within tumors, known as hypoxia, occurs more frequently in TNBC-BM. These conditions of oxygen deficiency seem to selectively support proliferation of breast cancer cells in the brain, thereby encouraging aggressive tumor cell behavior. Recent studies support the involvement of KDM1A in hypoxia. KDM1A also helps in the repair of DNA breaks, a process known as DNA damage response which limits the efficacy of radiation treatment. Further research is needed to better understand the role of KDM1A in TNBC-BM tumor progression, hypoxia-mediated responses, and DNA repair process.

Since KDM1A is highly expressed in several human cancers, there is significant interest in development of KDM1A inhibitor drugs, some of which are currently being tested in clinical trials for leukemia and lung cancer. However, these inhibitors are not suitable for TNBC-BM because they cannot cross the blood brain barrier to access the brain. **We developed a new KDM1A-specific inhibitor, NCD38, that efficiently reaches the brain and demonstrates minimal toxicity.** Preliminary studies show promising results that NCD38 reduces tumor growth of TNBC-BM and enhances survival of tumor-bearing mice. In this proposal, we will test the usefulness of KDM1A inhibitor NCD38 to treat TNBC-BM and determine the method by which it is able to accomplish this.

The **objective** of this proposal is to determine the functional role of KDM1A in TNBC-BM and develop a possible new clinical strategy to target TNBC-BM by employing KDM1A-specific inhibitor NCD38. The **central hypothesis** of this study is to demonstrate that KDM1A is essential for TNBC-BM cell survival and growth, KDM1A plays a key role in TNBC-BM hypoxic responses and DNA repair, and that inhibiting KDM1A using NCD38 can promote cancer cell death, attenuate hypoxic responses and DNA repair, and thus lead to a decrease in TNBC-BM growth. We will test this hypothesis using two aims. **In aim1**, we will test the efficacy of KDM1A inhibitor NCD38 in killing TNBC-BM cells and evaluate its therapeutic efficacy alone or in combination with radiation therapy to reduce TNBC-BM progression *in vivo*. **In aim2**, we will define the mechanism by which KDM1A inhibitor NCD38 exerts anti-tumor effects on TNBC-BM cells using studies that look at global gene expression of cancer cells, and test whether NCD38 mitigate radiation induced DNA break repair and hypoxia-mediated responses in TNBC-BM.

Successful completion of this proposal will uncover KDM1A-mediated epigenetic signaling in TNBC-BM that can potentially be targeted with novel KDM1A inhibitor NCD38, either alone or in combination with existing treatments such as radiation therapy, to improve outcomes for TNBC-BM patients. Knowledge from this proposal may lead to future studies and clinical trials in the coming years focusing on KDM1A inhibitors for treatment of TNBC-BM.