Public / Lay Abstract

Title: Altering the Metabolic Tumor Microenvironment to Impede Breast Cancer Brain Metastasis

Brain metastasis, a common complication in patients with advanced cancer, develops when cancer cells spread from a primary tumor to the central nervous system. Every year, among the 300,000 patients newly diagnosed with breast cancer in the United States, up to 20% will develop symptomatic brain metastases. Unfortunately, brain-metastatic breast cancers do not respond well to any type of currently available treatments, and fewer than 20% of breast patients with symptomatic brain metastases survive for longer than 1 year. In this new era of successful targeted therapies and immunotherapies, primary breast tumors are well controlled, and patients can live much longer, however, brain metastasis incidence increased up to 30% when breast cancer patients have disease recurrence later. Therefore, more attention needs to turn to treating brain metastasis. Patients with a limited number of brain metastases could benefit from combination treatment of their brain lesions with both improved quality of life and longer survival. Consequently, there is an urgent need to identify therapeutically targetable factors that promote breast cancer brain metastasis. Identifying these factors will guide discovery of more effective treatments for brain metastasis.

Tumors transform the tissues around them, creating their own tumor microenvironment (TME), which they use to establish a supply of nutrients and avoid being eliminated by host immune responses. In the brain, the TME provides nutrients that support the outgrowth of metastatic cancer cells. Therefore, treatments blocking the nutrient supply to inhibit the outgrowth of metastatic cells should be effective for controlling brain metastasis. Glutamine is a reliable and effective target for brain metastasis because it is critical in regulating cancer cells' dormancy, survival and proliferation. We found that brain-seeking breast cancer cells can hijack glutamine released from specialized brain cells (astrocytes) and grow quickly in cell culture media containing glutamine at the same concentration as in the brain. When we blocked brain-seeking cancer cells' uptake of glutamine with glutamine antagonists or glutaminase inhibitor, cancer cell proliferation was dramatically inhibited and brain metastases growth in mice were suppressed as well.

Therefore, we **hypothesize** that avid glutamine uptake promotes breast cancer brain metastasis and that drugs that inhibit glutamine uptake or utilization may be effective new treatments for breast cancer brain metastasis. We propose two Specific Aims to investigate whether targeting glutamine utilization will effectively treat breast cancer brain metastasis. In **Aim 1**, we will use multiple breast cancer brain metastasis mouse models to further investigate whether two key proteins of glutamine metabolism, SLAC1A5 and GLS, promote brain metastasis and understand the biological mechanisms by which they do so. In **Aim 2**, we will conduct preclinical trials in mice to test the efficacy of targeting glutamine with a clinically in-development drug named CB-839 and a glutamine antagonist, JHU083, for the treatment of breast cancer brain metastasis. Because we have found that blocking glutamine uptake also inhibits cancer cells evading the immune system and avoiding to be eliminated, we will also test whether CB-839 and JHU083, by blocking glutamine metabolism in cancer cells, may make brain metastases more sensitive to the anti–PD-1/anti-CTLA-4 immunotherapies and natural killer (NK) cell therapies. Specifically, we will test whether combining CB-839 or JHU083 with anti–PD-1/anti-CTLA-4 antibody or NK cell treatments can better inhibit the growth of brain metastases and prolong the survival of mice bearing brain metastases. If these studies are successful, our findings could be quickly translated to clinical trials.

This research will produce novel and deep insights into how brain metastases utilize glutamine in the brain and may bring about a new and effective metabolic-modulating therapy for breast cancer brain metastasis. Ultimately, we expect that it will lead to new and better treatments for breast cancer brain metastasis, which will prolong patients' survival and improve their quality of life.