

Public Abstract

In this new era of personalized cancer therapies, brain metastasis is a major challenge. Of 1.6 million annually diagnosed breast cancer patients, 10%-16% will develop symptomatic brain metastases. Sadly, although recent advances in targeted cancer therapies and immuno-therapies lead to better outcomes for patients with primary breast cancers, these patients have increased incidences (>30%) of brain metastasis at disease recurrence. It is devastating that brain metastatic breast cancers are refractory to almost all current treatments, and have a <20% one-year survival rate. A major reason for such a dreadful prognosis is that, efforts by the research community until now have focused mostly on primary breast cancer. Breast cancer metastasis, especially brain metastasis, however, remains understudied and underfunded, and as a result, there are NO effective treatment strategies tailored for brain metastasis. Consequently, there is an urgent need to identify therapeutically targetable factors that promote breast cancer brain metastasis, which can guide discovery of more effective treatment for brain metastasis.

To discover novel therapeutically targetable factors that promote breast cancer brain metastasis, we focused on kinases, a group of proteins that regulate a wide spectrum of cancer cell events that are critical for cancer progression and metastasis. We have screened 354 human kinases and identified a kinase, named CDK5, as a brain metastasis-promoting factor. In support of this finding, previous studies also showed that increased CDK5 level in breast cancer is significantly correlated with lower metastasis-free survival in breast cancer patients. Therefore, we **hypothesize** that CDK5 activation promotes breast cancer brain metastasis and CDK5 inhibitors may be developed as new therapeutics to treat breast cancer brain metastasis. Specifically, we propose two Aims to investigate the clinical translation value of CDK5 as a therapeutic target for the treatment of breast cancer brain metastasis. In Aim 1, we will use multiple breast cancer brain metastasis mouse models to further confirm the brain metastasis promoting function of CDK5 and understand the biological bases. In Aim 2, we will conduct pre-clinical trials to test the efficacy of inhibiting CDK5 with a clinically-applicable and blood-brain-barrier penetrating drug, named roscovitine, for the treatment of breast cancer brain metastasis in mouse models. Notably, combination treatment of roscovitine and sapacitabine has been tested in a phase I study in patients with advanced solid tumors (NCT00999401). Unfortunately, patients with previously untreated central nervous system (CNS) metastases or progressive CNS metastases are **excluded** from the trial. Thus, we cannot assess outcomes of roscovitine in inhibiting brain metastasis using data from this trial in which no patients with CNS metastasis were treated. However, our novel finding that CDK5 promotes brain metastasis warrant experimentally testing the potential effect of roscovitine on inhibiting brain metastasis, which has not been previously considered by other investigators. If successful, positive findings from our efforts can be translated to clinical trials in near future using roscovitine to treat breast cancer patients' brain metastases.

Currently, as NO targeted therapy is available for brain metastasis, this research may lead to the first generation of brain metastasis specific targeted therapies that can be rapidly delivered to breast cancer patients having brain metastasis, prolong their lives and improve their quality of life.