

## Public Abstract

While many advances have been made in recent years in the treatment of breast cancer, more than 40,000 women in the United States still die each year from this disease. This is because breast cancer cells that spread to distant organs, a process known as metastasis, are very difficult to treat. Breast cancers primarily metastasize to the bone, lung, liver and brain; and for breast cancer patients with metastatic disease, overall survival is 2-5 years from the time of diagnosis. The most aggressive breast cancer subtypes have higher levels of lung metastases, and when tumors metastasize to the lung, survival drops to only 13 months. Therefore, it is critical that lung metastasis-specific treatment strategies are found to treat patients with metastatic disease. The **overall goal** of this proposal is to identify cells or factors within the lung surrounding metastases that could be used as lung metastasis-specific therapeutic targets and/or prognostic indicators of disease burden.

My **previous studies** were conducted using breast cancer mouse lung metastasis models, the only effective way of studying metastasis in the laboratory. These studies found that cells in the lung surrounding metastases become activated as metastases grow. This activation was characterized as a type of chronic, inflammatory wound repair, with similarities to what is observed in the lungs of patients with chronic inflammatory lung diseases such as asthma. Roflumilast is an anti-inflammatory drug FDA-approved to treat lung diseases such as asthma that are associated with inflammation. My preliminary study using a metastasis model demonstrated that mice treated with roflumilast had decreased metastatic outgrowth compared to control treated mice. Interestingly, normal lung cells (called lung type II alveolar epithelial (AT2) cells), which play a critical role during wound healing, are also especially activated during metastatic outgrowth. My data show that during metastatic progression there is a change in the factors that are secreted by these lung cells, and based on previously published data, these changes are likely to promote the growth and survival of metastases within the lung. In particular, the gene surfactant protein b (*Sftpb*/SP-B) is downregulated during metastatic outgrowth. In lung cancer, this factor is known to inhibit tumor growth and is associated with a positive prognosis. My preliminary study showed that SP-B supplementation using Infasurf, a SP-B-containing therapy that is currently FDA-approved for use in SP-B deficient premature infants, inhibited breast cancer cell growth in culture, suggesting that this may be another lung specific drug that could be repurposed for use in the treatment of breast cancer lung metastases. Together my data suggest that breast cancer lung metastases activate adjacent lung cells which, in turn, may support metastatic growth, and I **hypothesize** that targeting the activated metastatic lung with repurposed therapies used to treat other common lung diseases/ailments could effectively inhibit metastatic outgrowth and eliminate the mortality associated with metastatic breast cancer to the lung.

The **first aim** of this application will examine whether the anti-inflammatory drugs roflumilast and cilomilast, which are currently FDA-approved for other purposes, could be repurposed for use in the treatment of breast cancer lung metastases. In addition, since roflumilast has previously been shown to enhance the sensitivity of tumor cells to chemotherapy, this aim will investigate if combination therapy, with roflumilast and chemotherapy, is effective in inhibiting metastatic growth in the lung and therefore improving standard of care therapy. The **second aim** of this application will determine the value of SP-B supplementation as a therapeutic strategy in treating patients with lung metastases. It will further investigate how levels of the lung-specific factor SP-B change throughout metastatic progression to determine if SP-B levels are directly related to metastatic burden. Currently, lung metastases are diagnosed using imaging techniques such as chest x-rays or computed tomography (CT) scans, which can only visualize sizable metastases. Data from this aim will benefit patient survival by allowing for earlier diagnosis/treatment of lung metastases by looking at SP-B levels within the blood. Finally, while experiments in aims one and two will be performed in mouse models of metastasis, the **third aim** will examine blood and metastatic lung tissue from breast cancer patients to determine if the lung is activated surrounding metastases in patients in a way similar to what is observed in mouse models. This will be helpful to determine if the therapies proposed in aims one and two will also be effective in patients.

By repurposing already FDA-approved drugs, the clinical trial process will be significantly shortened and the benefits to patients will be expedited. Taken together, this application will address several aspects of lung metastasis treatment that are lacking in the clinic, and the results from this project have the potential to greatly improve the survival of breast cancer patients with lung metastases.