Targeting epigenetic regulator PRC2 as a therapy for established metastasis

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Breast cancer affects more than 1.7 million individuals a year worldwide, with approximately 500,000 deaths. In the US over 230,000 are diagnosed resulting in 40,000 deaths annually. Importantly, >90% of this mortality is a consequence of metastatic disease that is resistant to adjuvant therapies. Particularly, patients with triple negative breast cancer (TNBC, lacking receptors ER, PR and Her2) have the worst outcome due to high rates of metastasis compared to non-TNBC counterparts. Standard cytotoxic chemotherapy and radiation are the only approved therapeutic options for women with TNBC, however, these treatments are usually ineffective. Several new agents that target angiogenesis, DNA repair or cell proliferation are being tested currently. However, clinical results with these agents have been suboptimal. **Despite the clinical significance, there has been little progress towards the treatment of metastasis. As a consequence there is a conspicuous lack of FDA approved targeted anti-metastatic therapies.**

Our focus is on a subset of advanced Stage IV breast cancer patients who present distant metastases at the time of initial diagnosis of a primary cancer. Others, who have no detectable metastasis during primary diagnosis, have an increased probability of developing metastasis as a result of recurrence. **Therefore, our goal is to identify and develop a "mechanism based" effective targeted therapy to shrink and eventually eliminate established metastases.** In this proposal, we will seek to develop the epigenetic factor EZH2 as a viable therapeutic target, as patients with increased EZH2 expression present the worst clinical outcome including metastatic recurrence, disease free and overall survival. Importantly, we have found that specific blockade of EZH2 catalytic activity with a potent drug markedly controlled growth of metastatic lesions. We have identified a specific population of cancer cells that are sensitive to the EZH2 drug. Importantly, these cancer cells have an increased potential for metastasis and exhibit resistance to chemotherapy. This is a critical finding, as chemoresistance constitutes a major barrier in the treatment of patients living with metastatic disease.

We hypothesize that EZH2 is linked to chemoresistance and metastasis, and that specific inhibition of EZH2 catalytic activity in combination with chemotherapy can be developed into a clinically viable anti-metastatic approach. We will test the hypothesis by using a combination of pharmacological and genetic approaches that specifically block EZH2 catalytic activity in preclinical models of metastatic TNBC. We will also identify EZH2 signaling pathways so that "mechanism-based" anti-metastatic therapeutic strategies can be designed. We propose to achieve the following objectives; 1) Determine the mechanisms by which EZH2 blockade impacts metastasis, 2) Evaluate if EZH2 inhibition synergizes with chemotherapy to eliminate metastasis, and 3) Determine efficacy of EZH2 inhibition in a panel of metastatic TNBC patient derived xenograft models. Our ultimate goal is to eliminate the mortality associated with metastatic breast cancer, and revolutionize treatment regimens by replacing them with ones that are more effective, less toxic, and impact survival.

Potential Impact. Advanced Stage IV breast cancer patients present distant metastases at the time of initial diagnosis of a primary cancer, or as a result of metastatic recurrence. As a consequence, an estimated 155,000 women in the United States are currently living with metastatic breast cancer (ASCO post 2017). Our goal is to exploit the catalytic activity of EZH2, as this activity is amenable to selective pharmacological inhibition and clinical translation. Equally important is the finding that EZH2 inhibition may overcome chemoresistance, which constitutes a major barrier in the treatment of patients living with metastatic disease. GSK126 is specific and potent inhibitor of EZH2 HMT with known pharmacokinetics and toxicity profiles, and is currently in Phase II trials of primary lymphoma. We expect that the preclinical data obtained from these studies will generate unique translational opportunities, and may allow this potential epigenetic medicine to move from bench-to-bedside with accelerated pace.