Public Abstract

Despite decades of breast cancer research into fundamental mechanisms, drug development, and early detection, breast cancer remains the second deadliest cancer for women. The chief cause of breast cancer mortality is metastatic disease, or the spread of cancer cells from the primary tumor in the breast to distant organs such as the lung, bone, liver, and brain. Whereas numerous drugs have been developed to combat breast cancer growth, both in the primary breast tumor as well as the metastatic site, these therapies are rarely curative as the cancer cells themselves are highly mutable, and often develop resistance to the currently approved targeted and cytotoxic therapies. Rather than targeting the cancer cells, therapeutics that seek to re-activate the immune system as living drugs against breast cancer cells offers the best hope for a cure to metastatic breast cancer, as has been witnessed with immunotherapies such as Keytruda™ in metastatic melanoma and lung cancers.

Recent research has demonstrated that breast cancer cells subvert the immune system in their local environment to dampen the anti-tumor immune response, making immunotherapies such as Keytruda™ ineffective. This immune subversion is performed through the education of naïve immune cells into an immunity-attenuating cell called a Regulatory T cell (T_{reg}). Here we propose to understand how this education of T_{regs} takes place within the metastatic breast tumor, with a particular focus on a new enzyme that has shown importance in generating T_{regs} in other diseases. By removing this enzyme in genetic models of breast cancer, we will seek to understand if this enzyme can be targeted to enhance the efficacy of immunotherapy in order to eliminate metastatic breast cancers. We have further developed molecular compounds with the ability to specifically inhibit this enzyme; we will test these compounds for their ability to re-stimulate anti-tumor immunity, either alone or in combination with immunotherapies approved for other cancers.

In performing this research, we aim to both i) Understand the importance of immune regulation during metastatic breast cancer and ii) Develop proof-of-concept data for a new molecular target whose inhibition by our recently developed small molecule inhibitor may help metastatic breast cancer patients. In addition, this research will develop tools that enable new avenues of research and drug development to benefit stage IV metastatic breast cancer patients. Ultimately, we believe that findings from this research will lead to the development of a new curative therapy for stage IV breast cancer patients.