

Public/Lay Abstract:

Immunotherapy works by re-training the body's immune system to fight cancer. This type of therapy holds great promise to help people with metastatic breast cancer live longer with fewer side effects from ongoing therapy or progressive disease. When people get sick, the body's immune system works to recognize foreign cells causing infection and kills them. However, in the case of cancer, the tumor cells send signals to the body to turn the immune system off thus preventing the immune cells from doing their job of tumor elimination. Eventually, the lack of immune response enables tumor growth and, in many cases, metastatic spread. A long-term goal of immunotherapy is to significantly prolong the lives of patients with breast cancer without the toxicity of traditional chemotherapy. Unlike chemotherapy, the beneficial effects of immunotherapy continue to work even after treatment has stopped. It is our hope that these lasting effects translate to years of improved quality of life and disease stability even in cases where breast cancer has spread to other organs in the body/metastasized.

One hurdle that needs to be overcome is to broaden the approval of immunotherapy to include more patients diagnosed with breast cancer. To help bring this life-saving therapy to more patients, we need to determine how to improve its effects. In the short term, my work will contribute to understanding how to improve the beneficial effects of immunotherapy by combining it with novel drugs that target immune suppressor cells. If we can remove the signals suppressing the body's natural anti-tumor response, then we will likely improve the response rates to immunotherapies called checkpoint inhibitors that are already used widely to treat other tumor types such as melanoma and lung cancer. The other benefit of this approach would be that it is less toxic and prolongs disease free survival. Patients with metastatic breast cancer often have to endure the side effects of numerous different classes of drugs, chemotherapy as well as other targeted therapies, as their cancers become resistant to each subsequent line of treatment. If we can find a way to activate the immune response in patients, their duration of response could be drastically improved and thus, their quality of life improved as well. I have designed experiments that will investigate how to maximize the benefit of the body's own immune system and minimize toxicity.

One category of immune cells identified within tumors are called immunosuppressor cells which are recruited by tumors to send signals that keep the beneficial anti-tumor immune cells out. Our goal is to identify and characterize the immunosuppressor cells that reside inside of tumors and determine how to control the signaling that shuts down the anti-tumor immune response. We hope to contribute to the development of novel treatment strategies that will target immunosuppressor cells within tumors in order to prevent suppressive signaling. By developing novel combinations with immunotherapy, we hope that patients will not experience as many side effects as they do with traditional chemotherapy and thus can have better quality of life.

We will also determine if the immunosuppressor cells identified within metastatic tumors are different from those found inside primary breast tumors. More specifically, we will start by investigating breast tumors that have metastasized to the lung and compare these with tumors growing within the breast. It is possible that the immunosuppressor cells infiltrating breast tumors growing within the lung are different from those growing within the breast and thus the efficacy of novel therapeutic combinations will vary. This is important to help develop strategies to personalize treatment based on disease burden.

Over the past 5 years I have led a team of physicians and scientists across 5 universities to study the novel combination of a histone deacetylase inhibitor entinostat, with checkpoint inhibitors nivolumab and ipilimumab in patients with advanced cancer, including many patients with breast cancer. We observed a number of responses in patients with breast cancer that led to an increase in overall survival. There is still much to understand about the changes within the tumor that led to these responses. My lab employs cutting edge technologies such as single cell RNA sequencing, which decodes the gene expression profiles of each individual cell in a tumor sample, giving us a near-complete picture of all the different cells present and their characteristics. We can use this technology to evaluate thousands of genes in tens of thousands of cells and track each cell following different types of experimental treatments. This type of technology, as well as other cutting-edge experiments, will help us determine with great precision the developmental origin, susceptibility to treatment and overall functional roles of different immune cells within tumors and metastatic sites. Once we identify the immunosuppressor cells that are most likely contributing to response, we will perform experiments to understand how to further manipulate the signals within these cells to promote an anti-tumor immune response. Overall, these discoveries could revolutionize how we treat patients with metastatic breast cancer and help people live longer, with an improved quality of life.