METAvivor Research Award

Applicant: Dr. Andrei Bakin, Associate Professor of Oncology, Department of Cancer Genetics and Genomics;
Co-Applicant: Dr. Scott Abrams, Professor of Oncology, Department of Immunology, Roswell Park Comprehensive Cancer Center
Title of project: A Novel Combination Therapy to Improve Treatment of Metastatic Breast Cancer

PUBLIC/LAY ABSTRACT

Over 3 million women are currently diagnosed with breast cancer in the United Sates and over 155,000 are living with stage IV metastatic breast cancer (MBC). The five-year survival rate for MBC patients is less than 25 percent with over 40,000 deaths expected this year. Patients with MBC of the triple-negative breast cancer [TNBC; negative for the estrogen, progesterone, and HER2 receptors ($ER^-/PR^-/HER2^-$)] subtype have the worst prognosis. Currently, MBC is not curable, and the mainstay chemotherapies have limited long-term clinical benefit. Thus, efforts to develop newer therapies or novel therapeutic combinations are urgently needed. To that end, chemotherapy has now been combined with a completely different class of oncologic agents, known as immune checkpoint inhibitors (ICIs) for use in metastatic TNBC. ICIs, in contrast to chemotherapeutics, do not have direct anti-cancer effects, but rather they kill cancer cells indirectly by unleashing the power of an immune cell population known as the cytotoxic $CD8^+$ T cell. So far, in metastatic TNBC, such a combination regimen improves patient outcome (as measured by progression-free survival), but only for a few extra months when compared to chemotherapy alone. Despite the limited improvement, these findings not only established the basis for the use of ICIs in metastatic TNBC, but also have inspired the field at-large to develop more effective therapeutic combinations.

We now know that a major barrier that diminishes the efficacy of ICIs is a cancer-driven process known of immune suppression. Immune suppression is a complex process, but essentially it acts as a brake to ICIs, the accelerator. Major components of this suppressive network are myeloid populations, namely myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) which are a type of blood cell induced in cancer, including MBC, that potently shutdown $CD8^+$ T cell-mediated killing. Therefore, it makes sense that strategies which hinder the production of MDSCs and TAMs will boost anti-cancer $CD8^+$ T cell activity in response to ICIs.

Thus, our proposal explores a novel therapeutic approach to block the production of MDSCs and TAMs in preclinical models of MBC in an effort to enhance the therapeutic potency of ICIs. Our preliminary data demonstrate that if we inhibit the activity of a protein called 'p38 protein kinase' or p38 for short, in MBC cell lines using a clinically relevant agent, we significantly reduce lung and liver metastasis, which is accompanied by reductions in MDSCs and TAMs and reciprocal increases in the accumulation of $CD8^+$ T cells within the cancer tissue. Based on these findings, we *hypothesize that the combination of ICIs with an agent which targets p38 in MBC will potently inhibit metastasis and translate to improved survival rates. We further hypothesize that the mode of action of the p38 inhibitor is to impede the ability of MBC cells to recruit MDSCs and TAMs, thereby, enhancing the efficacy of ICIs to activate anti-cancer $CD8^+$ T cells*. To test this hypothesis, we will use several preclinical models of metastasis that mimic clinical settings of stage IV MBC. Successful completion of this study will provide a novel mechanism of, and novel application for, anti-p38-targeting agents to substantially reduce the burden of MBC. Our discovery has the potential to rapidly lead to a Phase I clinical trial at our cancer center with the proposed drug combination for MBC patients, given the availability of both classes of drugs already in clinical use, but never combined in this disease setting.