Targeting an immune-suppressive cholesterol metabolite in the treatment metastatic breast cancer.

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Despite increased survivorship among patients, breast cancer remains the most commonly diagnosed cancer among women. Moreover, breast cancer is the second leading cause of cancer related death in women. Irrespective of subtype, breast cancer mortality is most often due to the metastatic recurrence of the disease. A recent report by the National Cancer Institute has found that more women than ever before are being diagnosed with and living with Stage IV (metastatic) breast cancer. Indeed, recurrence with metastatic breast cancer weighs heavily on the minds of breast cancer survivors. Unfortunately, there are currently no targeted therapies to treat this stage of disease, forcing clinicians to resort to cytotoxic chemotherapy and/or radiation, both of which having only limited success. Therefore, there is urgent need for studies that will lead to novel therapeutic interventions for the treatment of this stage of disease.

With this in mind, we decided to identify potential novel therapeutic targets by reviewing epidemiologic evidence that identified factors associated with poor prognosis. In this regard, women with metastatic breast cancer and elevated total cholesterol have a poor prognosis. This is important since cholesterol synthesis and metabolism is an area amenable to drug intervention. For example, statins are FDA approved and highly effective at reducing cholesterol levels in patients at risk of cardiovascular disease. Importantly, many studies now indicate that breast cancer survivors on statin therapy have an extended time to recurrence. Our work in mice has confirmed that when placed on a high cholesterol diet metastatic lesions grow and spread more rapidly, while mice on statins are protected. Interestingly, we have found that it is not cholesterol *per se*, but its metabolite 27-hydroxycholesterol (27HC) that promotes metastasis. 27HC has previously been shown to behave as a hormone by modulating the activities of both the estrogen receptors and liver X receptors (ERs and LXRs). Our preliminary data suggest that through its actions on these receptors, 27HC acts on immune cells called neutrophils to suppress the activity of cytotoxic T-cells, immune cells that normally have anti-cancer activity. **Therefore, we hypothesize that by suppressing acquired immune activation, 27HC promotes the pathologic progression of metastatic breast cancer.**

Immune checkpoint inhibitor therapy has revolutionized how we think about cancer immune-therapy. Its success in metastatic melanoma and other cancers has provided strong rationale for their investigation in the treatment of metastatic breast cancer. However, to date such treatments have had limited clinical success. T cell abundance and infiltration has been reported as one prognostic factor associated with checkpoint inhibitor success. Our data indicates that 27HC dramatically impairs T-cell activation, suggesting that targeting this axis may re-educate immune cells, thereby promoting the efficacy of immune checkpoint inhibitors.

We will test our hypothesis in the following specific aims: (1) *Elucidate the mechanisms by which 27HC impairs the anti-tumor immune response*. Using state-of-the-art mouse models, we will definitively test the immune-suppressive effects of 27HC. In addition, since 27HC is a known ligand of the ERs and LXRs, we will probe the relative contribution of these receptors to the immune-suppressive phenotype. This work will serve as the foundation for future drug development simultaneously targeting both the ERs and LXRs.
(2) *Evaluate the therapeutic utility of combining immune-checkpoint inhibitors with either inhibitors of HMGCoA-reductase (statins) or CYP27A1 (27HC synthesis), for the treatment of established metastatic breast cancer*. Using humanized mouse models susceptible to statin therapy, we will test the efficacy of combining a statin with an immune checkpoint inhibitor. Furthermore, we will also test the efficacy of a small molecule inhibitor of the enzyme responsible for the synthesis of 27HC in combination with checkpoint inhibitor therapy. This is a highly translational aim which we hope will impact clinical care in the near future.

Expected Outcomes: A series of integrated experiments will determine both the cellular and biochemical mechanisms by which 27HC impacts the pathophysiology of breast cancer metastasis. This work will serve as the rationale and foundation for the clinical development of combination therapy targeting cholesterol metabolism and immune-checkpoints. This research is of significant importance, given the current prevalence of hypercholesterolemia, that the majority (>90%) of mortality associated with breast cancer is due to metastatic disease, and the poor efficacy of currently available therapies for the treatment of metastatic breast cancer.