Lay Abstract

Breast cancer is one of the most common cancer types in women, accounting for over 30% of all cancer incidence in women in the United States. Although significant progress has been made in the understanding of this disease, there are two main issues that still confound their treatment - the spread of the cancer to other organs of the body (metastasis), and resistance to chemotherapy, which results in the recurrence of tumors.

Through research we now know that the ability of breast cancers to spread and to be resistant to chemotherapy can be attributed to the inherent heterogeneity present with the tumor i.e., the presence of multiple subpopulations of cells within the tumor that are non-identical. This heterogeneity confounds our ability to treat tumors as not all cells respond to therapy in a similar fashion. Thus, an important part of developing novel therapies for cancer includes understanding this heterogeneity and designing novel therapies to combat the various cell subpopulations that comprise a tumor.

The proposed research focuses on how to reduce levels of tumor heterogeneity such that they would respond better to chemotherapy and have reduced metastatic potential. To do this, we propose to implement a program that allows more aggressive tumor cells to transition to becoming more benign counterparts, referred to as a mesenchymal-to-epithelial transition (MET). From our observations, inducing MET, akin to inducing a form of differentiation, leads to a reduction in the metastatic load in models of triple negative breast cancer. In this study we propose to use eribulin, an FDA approved drug that is currently used as third-line therapy for metastatic breast cancer, as an MET-inducing agent, and to study its effects in late-stage tumors that form overt metastasis. Our preliminary data indicate that treatment with eribulin is able to induce the differentiation of metastatic nodules and render them more benign. In this study we propose to test the ability of eribulin to impair the conversion of micrometastases to overt macrometastatic colonies and study the mechanism by which it is able to exert these effects on tumor progression.

In achieving these aims, we would have made a significant contribution to the field of breast cancer research, one that has the potential to be translated into clinical outcomes in the future. Given that eribulin is already FDA approved for the treatment of metastatic breast cancer, our results can be translated more rapidly into clinically useful protocols that can be easily implemented.