

METAvivor Early Career Investigator Lay Abstract

Breast carcinoma is the most common malignancy and the second leading cause of cancer associated deaths in women. While significant advances have been made in the treatment of patients with localized breast cancer, the survival for patients diagnosed with disseminated disease has not significantly improved for the past three decades. One explanation for this current dilemma is the underappreciation for the unique genetic and biochemical events that distinguish cancer cells composing primary breast tumors from metastatic breast cancer cells. Another contributing factor for this disparity in knowledge and outcomes for patients with metastatic disease is historical bias against the study of non-coding genes in these processes. Because of several failed clinical trials after initial discovery, the exploitation/utilization of these genes as therapeutic targets has been taboo in the past decade. Our lab studies the role of ncRNA in tumor initiation, progression, and metastasis. One class of ncRNA studied extensively in our lab is microRNA (miRNA).

miRNA are small, noncoding RNA genes that negatively regulate the levels of other genes. It is the conviction of our laboratory, and many others in the field, that these genes and being underutilized clinically and can be instrumental for improving patient outcomes and pre-clinical studies in this area will ultimately lead to a cure for breast cancer metastasis. Specifically, we believe that a focused approach examining well known metastasis promoting genes that have proven “undruggable” for an array of reasons, can be targeted using miRNA. In this proposal, we examined for miRNA binding sites in canonical oncogene *SRC*. *SRC* is the first discovered oncogene and belongs to the *SRC* family of kinases (SFKs) which are non-receptor signaling proteins. SFKs are genes that can act in multiple different ways and are involved in many cellular processes. Changes in *SRC* signaling contributes to breast cancer cell proliferation, survival, migration, invasion, and metastasis. *SRC* also interacts with other metastasis promoting genes (EGFR, HER2, PDGFR, IGF-1R, HGFR) (4) and has been a goal to target therapeutically but there has been little success in these efforts.

We've identified a novel miRNA that targets *SRC* (*SRCamiR-1:SRC associated miRNA-1*) and propose that this miRNA can be used to treat metastatic breast disease. *SRCamiR-1* levels are lower in patient breast cancer samples when compared to normal breast tissue. To determine if *SRCamiR-1* predicts survival, individuals with breast cancer had their breast tumors analyzed for *SRCamiR-1* and we observed that when patients lose *SRCamiR-1* expression in their breast tumor, survival is significantly worse compared to patients who have higher *SRCamiR-1* levels in their breast tumors. We've found that when we genetically add back *SRCamiR-1* to aggressive breast cancer cells, these cells are inhibited in their migratory and invasive abilities: processes important for cancer metastasis. When we further test these cells that have *SRCamiR-1* levels restored for metastasis in animal models of breast cancer metastasis, we see nearly 100% suppression of metastasis.

For this proposal, we seek to test whether *SRCamiR-1* re-activation in established breast cancer metastases will lead to tumor regression. To achieve this, we will use our established animal models of breast cancer metastasis and re-activate *SRCamiR-1* using both a genetic and pre-clinical therapeutic folate modified *SRCamiR-1* approach to cure metastatic disease. We have assembled a team of international experts to assist us in this project that we believe will lead towards developing new therapies for stage IV metastatic breast cancer patients and ultimately lead toward a cure for this deadly disease.