**PUBLIC ABSTRACT**

While remarkable advances have been made in the treatment of primary breast cancer, breast cancer metastasis (the dissemination and spread of cancer cells to distal sites in the body) remains largely incurable and is what accounts for approximately 90% of patient deaths. Metastatic breast cancer cells have the capacity to invade both lymphatic and blood vessels and spread to distant organs such as lung, liver, brain and bone, and these cancer cells remain resistant to conventional breast cancer treatments such as chemotherapy and anti-estrogen therapies. Thus, patients diagnosed with metastatic disease have extremely poor outcomes, with only 5-10% of patients surviving 10 years after initial diagnosis. Despite extensive studies over the last four decades, there are no therapies that can be said to cure breast cancer metastasis, and therefore there has been little improvement in the survival of these patients. New treatment approaches are therefore urgently needed to target aggressive primary cancers prior to metastasis and metastasis once it has occurred.

The proposed research seeks to study a novel drug named PMR116, a clinical-stage inhibitor that shows promise in blocking the malignant traits of metastatic breast cancer cells. The first of these mechanisms is Epithelial-to-Mesenchymal Transition (EMT), for which there is a growing body of evidence to support its role in the progression of metastatic breast cancer. The other mechanism, which is the focus of our work to date, is the production of specialized protein factories within breast cancer cells, known as ribosomes.

Our past studies have revealed that during metastasis, breast cancer cells start producing specialized ribosomes that help them to invade. We have now found that treatment with PMR116 blocks the production of these specialized ribosomes, and prevents EMT. This subsequently prevents metastatic spread to the lung and the viability of established metastases. These results are compelling evidence of the promise PMR116 holds for the prevention and treatment of metastatic cancer. It is important to note that a handful of studies are underway to address the use of this compound for cancer treatment, but importantly our proposed research repositions these drugs for metastatic breast cancer, and at doses far below those used in previous studies. Furthermore, our findings indicate that pharmacologically targeting ribosome production in metastatic breast cancer cells leaves normal tissues untouched, with very little normal tissue toxicity, indicating that these compounds can be both effective and minimally harmful as treatments. Finally, we have discovered that PMR116 inhibits ribosome production in the brain, which means that the drug can pass the blood brain barrier, a barrier which otherwise impenetrable against many drugs. This suggests that PMR116 may be effective for the treatment of breast cancer metastasis to brain, which is among the most swift and deadly forms of breast cancer metastases.

**The focus of the proposed research is to gain a deeper molecular understanding of specialized metastatic ribosomes that will inform the therapeutic targeting in human clinical trials, using clinical stage small molecule inhibitor PMR116 as novel means of halting breast cancer metastasis and targeting established metastases.**

In sum, with support from the Metavivor we will obtain key data about the anti-metastatic effects of PMR-116, specifically in metastatic breast cancer to the brain. This has not been investigated in vivo for PMR116 despite its clinical entry. Using the knowledge gained, we will PMR116 in the preclinical setting including dosing, schedule and mechanism of action in the metastatic breast cancer setting, in order to pursue the clinical development of this clinical stage small-molecule compound that have low toxicity and is efficacious. We believe our proposed research will lead the way to redeploy PMR116 in the clinic for treatment of metastatic breast cancer, which could mark a major turning point in improving the survival rate of breast cancer patients.