

## **Public (Lay) Abstract:**

Primary cancer, that is the first tumor to ever develop and be clinically detectable in a patient rarely kills the patient. This is because the initial lesions are removed in the vast majority of the cases by a surgeon. In fact, cancers commonly kill patients through the generation of secondary growths in other organs separate from where the original lesion was detected. These secondary growths or tumors are called metastasis and this represents stage IV cancer. These lesions originate from cancer cells that separated from the original tumor, like the breast, and gained access to the bloodstream to then spread and reach other organs where they grow. However, cancer cells do not grow immediately and can remain in a sleeping or dormant state for many years before growing again. What we discovered is that while some of these cancer cells that went on to produce a metastasis clearly were able to grow, many more remain sleeping in the same organ (lung or liver for example) where the metastasis grew in a stage IV cancer patient. Then when chemotherapy, radiation or other anti-proliferative (anti-growth) treatments are administered to the patient, while the growing tumors many times shrink, the dormant tumor cells that remain solitary or in clusters near those lesions that grew and then shrank upon treatment, may escape the chemotherapy simply because they do not divide. In addition, we discovered that lack of growth is not the only reason for escaping chemotherapy; dormant cancer cells can activate stealth and survival mechanisms that allow them to persist for a long time and avoid the effects of chemotherapy. We propose that these cancer cells are the ones that grow back, sometimes after long periods.

Our work will test how a signal found activated in dormant breast cancer cell models when blocked eradicate dormant cancer cells and maximize the effect of chemotherapy used to treat stage IV cancer. The target is a signaling protein called PERK that serves as a survival signal that allows cancer cells to adapt to different types of stress. We have identified selective blockers of PERK and it kills dormant cells in animals that also carry metastasis but does not attack the growing metastasis. We also discovered using the PERK blocker drug that the innate and adaptive immune system is reshaped and cells that promote metastasis such as neutrophils and macrophages are reduced in numbers in response to the decrease of a circulating cytokine (IL17) that activates these immune cells. Thus, the PERK blocker might stop metastasis by affecting the cancer cells directly or through the elimination of immune cells that support cancer and/or by restoring an immune response. We will test how combining PERK blockers with chemotherapy helps prolong the survival of animals with stage IV breast cancer. These studies will allow validating the hypothesis that treating both dormant and proliferative cancer cells in stage IV cancer will be beneficial for patients. These results would fuel next generation studies to discover new targets and optimize such therapies.