PUBLIC ABSTRACT

A majority of breast cancer related deaths worldwide occur as a result of the cancer spreading to one or more organs thereby becoming metastatic. Metastatic breast cancer kills over 40,000 patients a year in the United States. Although those with metastatic breast cancer are living somewhat longer, patients with breast cancer brain metastasis (BCBM) have not fared as well. In recent years, compared to single tumor cells, clusters of tumor cells have been shown to have a greater ability to spread to other organs. The interaction of tumor cell clusters with distant organs, particularly, the brain, is not well understood, making it extremely difficult to develop therapies that might be of benefit to the metastatic patient. To develop new therapeutic options, an improved understanding of the interaction of metastatic breast tumor cell clusters with the brain environment and the mechanisms governing their behavior is crucial. This research aims to create a modifiable three dimensional (3D) tumor microenvironment to study the behavior of brain metastatic breast tumor cell clusters, with a goal of identifying pathways responsible for tumor progression, and ultimately, opportunities for tumor targeting.

Current techniques to characterize the behavior of brain metastatic breast cancer cells *in vitro* typically employ two dimensional rigid plastic substrates that do not provide tissue-like conditions. The environment surrounding tumor cell clusters is known to play a key role in influencing whether or not tumor cell clusters will proliferate to establish metastasis, yet the precise roles of several signals in the brain tissue environment, including biophysical signals in conjunction with cellular signals, remain largely unknown. To this end, bioengineered 3D Jell-O like scaffolds will be used to culture brain metastatic breast tumor cell clusters and supporting cells such as astrocytes (a type of normal brain cell) will be incorporated into the scaffold mimicking features of the tumor environment in the brain. Scaffolds will be tuned by changing the stiffness spanning the range observed for native brain tissue and that observed for intracranially implanted breast cancer cells in mouse models, as well as the ratio of astrocyte to BCBM cells. We will quantify how brain metastatic breast tumor cell clusters respond to these environmental signals presented independently and subsequently identify culture conditions that allow them to stay in a dormant state as well as those that allow them to proliferate. We will also test the impact of tumor cell cluster size given the strong clinical significance of tumor size in disease progression.

For these conditions, we will perform genomics to identify a genomic signature governing the “proliferative” and “dormant” phenotype of brain metastatic breast tumor cell clusters. We will also validate key genes identified via genomics thereby identifying critical cell signaling associated with both proliferation and dormancy. If we successfully identify pathways mediating tumor progression, this may enable new tumor targeting strategies (i.e., new drug combinations targeting the pathways identified) thereby eventually enabling translation of these findings to the clinic. Such strategies have the potential to improve survival, positively impact quality of life and advance patient care, ultimately leading to a reduction in breast cancer mortality rates.