PUBLIC ABSTRACT

Breast cancer patients positive for human epidermal growth factor receptor 2 ($HER2^+$) are at a high risk of brain metastasis, even with adjuvant therapy. Compared to non-central nervous system metastases, brain metastases are associated with faster disease progression, shorter overall survival and lower quality of life. Brain metastatic relapses are observed in approximately fifty percent of the $HER2^+$ breast cancer patients. **HER2-targeting therapies on intracranial lesions are ineffective, and tolerable systemic agents aimed at eliminating residual cancer cells are needed for patients with metastatic $HER2^+$ breast cancer.** Identifying the genomic and metabolic alterations that brain resident cancer cells undergo during a metastatic outbreak is indispensable to develop strategies to target and eliminate metastasis.

We have addressed this knowledge gap by characterizing phenotypically stable brain metastatic cells from $HER2^+$ breast adenocarcinoma patients in xenografts and cell lines. Disseminated brain metastatic cells downregulate immune activating sensors, and escape host immune surveillance, mimicking clinical observations. Transcriptomic and metabolic profiles of brain metastatic cells revealed defining characteristics of these phenotypically divergent cancer cells. Brain metastatic cells have increased glycolytic flux and pharmacological inhibition of glycolysis resulted in reduced metastatic burden. Additionally, brain metastatic cells have acquired traits that aid escape from immune surveillance. **Our working hypothesis is that disseminated cancer cells in the brain with augmented glycolytic flux and aptitude to constrain innate immune surveillance give rise to overt metastasis.** In this proposal, we will use unique metastatic models for $HER2^+$ breast cancer brain metastasis developed by my lab to investigate and target determinants of brain metastatic cell survival and outgrowth**.**

We will **determine the impact of perturbing glycolytic flux during a metastatic outbreak on tumor cell survival and the surrounding brain parenchyma in metastatic mouse models and patient derived xenografts.** Brain metastatic cells are resistant to NK cell mediated cytotoxicity and escape NK driven immune surveillance by significantly increasing expression of transforming growth factor beta (TGF-β) family members. We will **define how TGF-β and Activin-A aid brain metastatic cells in escaping innate immune surveillance and test strategies to limit metastatic outgrowth by reactivating NK cells.**

Our preliminary results support the feasibility of these goals and we are well-positioned to achieve them given our expertise in modeling metastasis. The proposed studies will define the pathophysiological consequence of altering cellular energy determinants and reactivating innate immune surveillance on metastasis. They will also assess the potential of targeting these survival determinants of brain metastatic cells as therapeutic strategies to improve quality of life and survival outcomes in $HER2^+$ breast adenocarcinoma patients with brain metastasis.