Targeting Novel Tumor-Stroma Interactions in Breast Cancer Brain Metastases
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Brain metastases occur in ~10-30% of all metastatic breast cancer patients, yet surprisingly, there are still no set guidelines on how to treat breast cancer associated brain metastases due to the complete lack of approved therapeutics to target these lesions and the inability of most approved chemotherapeutics to effectively get into the brain. As such, patients are offered a combination of chemotherapy, whole brain radiation, stereotactic radiation and/or surgical resection, but even with aggressive treatment, the median survival is ~10 months, and quality of life can be greatly reduced from cognitive decline. The total absence of any guidelines from the National Comprehensive Cancer Network (NCCN) for managing women with breast cancer associated brain metastasis confirms the dire need for continued investigation into mechanisms of metastatic seeding and growth at this site. This proposal directly addresses this enormous clinical problem.

One main factor contributing to the ineffectiveness of current treatment strategies for breast cancer associated brain metastases is that both the primary breast tumor and their associated metastases are extremely complex. Not only do tumors contain the cancerous breast cells, but they also contain a number of other cell types that directly affect cancer progression and metastasis. Collectively, these cell types are termed the "tumor microenvironment". Similarly, in the metastatic organ, they are termed the "metastatic microenvironment". This microenvironment includes immune cells and endothelium (cells that line the interior of blood vessels), and of specific interest to this proposal, multiple cell types of mesenchymal origin. Mesenchymal cells in the breast include adipocytes (fat cells), pericytes (cells that surround the endothelium), and fibroblasts (cells that generate the structural matrix surrounding a cell). In the brain metastatic microenvironment, breast cancer cells integrate within a network of immune cells, endothelium, pericytes and neuronal cells such as astrocytes. Given that we know the microenvironment plays a critical role in cancer progression and metastases, the goal of this proposal is to identify important pathways within the metastatic brain microenvironment that can be targeted in new treatment paradigms for metastatic breast cancer patients.

In searching for such driver pro-metastatic pathways involved in breast cancer, our preliminary analyses uncovered a protein termed platelet derived growth factor receptor-beta (PDGFRβ). Interestingly this receptor is found primarily in cells of the breast tumor/metastatic microenvironment while PDGF-B, the protein that activates the receptor, is expressed primarily by the breast tumor cells. Our preliminary studies have revealed that high PDGF-B expression specifically correlates with the development of breast cancer brain metastases, however little is known about the function of this signaling pathway (PDGF-B to PDGFRβ) in metastatic progression to this site. Based on this preliminary data, we postulated that PDGF-B produced by some metastatic breast cancer cells activates PDGFRβ in the brain microenvironment and that PDGF-B to PDGFRβ signaling is essential for the growth and survival of these breast cancer cells in the brain. The experiments outlined in this proposal are designed to determine whether inhibiting this pathway may provide an important new avenue of treatment for some women with breast cancer that has metastasized to the brain. Another factor that has limited breast cancer metastasis research, especially brain metastasis, is the lack of appropriate in vivo models to study the complex interactions between tumor cells and the metastatic microenvironment. To overcome this limitation, our group has established a mouse model harboring hyper-active PDGFRβ signaling in the metastatic brain microenvironment. Our preliminary findings using these mice have revealed that upon intravenous injection with mouse mammary cancer cells, 50% of the mice with hyper-active PDGFRβ in their brain microenvironment display brain metastases, whereas normal mice are free of brain metastases. To our knowledge, this is the first known example where a single change to the brain microenvironment induces breast cancer brain metastasis.

In the current proposal, I will utilize this unique mouse model to test the efficacy of commercially available PDGFR inhibitors (e.g. imatinib, pazopanib, crenolanib) in treating established murine cancer growth in the brain. These experiments will exploit multiple murine metastasis model systems, wherein established brain metastases will be

confirmed by magnetic resonance imaging prior to therapeutic intervention directly mirroring the clinical setting. Furthermore, while the PDGF-PDGFRβ signaling axis may drive a subset of breast cancer brain metastases, other pathways active in the microenvironment are likely to support important breast cancer brain metastatic growth. As a second part of the proposal, we will study breast cancer patient tissue by analyzing ~30 brain metastases for important players actively engaged in the metastatic microenvironment. Factors that are pharmacologically targetable will be the subject of intense future research extending beyond this award period, with the ultimate goal of devising therapeutic strategies to effectively treat women who have developed brain metastases from breast cancer.