Public/Lay Abstract

Title: Targeting Neuronal Dopaminergic DRD4 Signaling in Brain Metastatic Breast Cancer

Rationale and Goal: When breast cancer spreads to the brain, it becomes a life-threatening condition known as breast cancer brain metastasis (BCBM), particularly devastating for patients with triple-negative breast cancer (TNBC). Unlike brain tumors that start in the brain, BCBM manipulates the brain's environment in unique ways to grow and resist treatments. Our research has revealed that aggressive breast cancer cells, such as those in TNBC, release signals that "rewire" brain cells (neurons) by enhancing a specific protein called DRD4. This protein makes neurons hyperactive, creating a supportive environment, or "niche," that helps cancer cells grow and escape a dormant (inactive) state where they are harder to treat. Our goal is to understand how DRD4 drives this harmful interaction between cancer cells and neurons and to test a drug, L-745,870, which blocks DRD4. By stopping this rewiring, we aim to slow cancer growth and keep cancer cells dormant, preventing them from forming deadly tumors in the brain.

Research Approach: We will use cutting-edge tools to study this process. First, we'll employ human brain-like models, called miBrains, which mimic the brain's complex mix of cells, to investigate how cancer cells alter neurons and test whether L-745,870 can reverse these effects. We'll also use mice with human breast cancer cells injected into their brains, tracking tumor growth with a high-powered MRI scanner to see if L-745,870 reduces tumors. Additionally, we'll examine brain tissue samples from patients to confirm that DRD4 is active in real BCBM cases. Our studies will focus on TNBC, which has a high risk of brain metastasis and few treatment options, but we'll also test other breast cancer types to ensure broad impact.

Anticipated Clinical Applications and Benefits: This research could transform treatment for stage IV BCBM patients, especially those with TNBC. L-745,870 is a promising drug because it has already been tested in humans for other conditions, showing it can safely reach the brain. By blocking DRD4, we expect it to shrink tumors or keep them dormant, potentially extending patients' lives. Our findings could lead to clinical trials testing L-745,870, offering a new therapy for BCBM patients who currently face limited options. We'll also identify signs (biomarkers) in patient tissues to predict which patients might benefit most from this treatment, paving the way for personalized medicine. Even as basic research, our work will reveal how breast cancer manipulates the brain, providing critical knowledge to develop new drugs that target this process, ultimately improving outcomes for those living with metastatic breast cancer.

Significance for Patients: For people battling stage IV breast cancer that has spread to the brain, this research offers hope. By targeting DRD4, we aim to disrupt the environment that fuels cancer growth, potentially slowing disease progression and improving quality of life. Our focus on TNBC addresses a critical need for patients with this aggressive subtype, and our findings could benefit others with brain metastases. This work brings us closer to new, effective treatments, offering a brighter future for those facing this devastating disease.