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PUBLIC/LAY ABSTRACT

RATIONALE
As treatments for breast cancer improve and patients survive longer, the prevalence of breast-to-brain metastasis increases, severely affecting patients' function, quality of life, and overall prognosis. 10-15% of women with metastatic breast cancer develop brain metastases. However, rates as high as 30% (HER2+) and 50% (triple negative) are observed. Patients with breast cancer brain metastases are frequently excluded from clinical trials, and standard treatment options are often ineffective. Thus, there is an urgent need to understand the biology of breast cancer brain metastases for prediction of patient risk and discovery of novel drug targets for improved treatment of the already metastasized patient.

One potential strategy to halt the progression of breast cancer brain metastases is through modulation of the space surrounding the brain tumor (i.e., the tumor microenvironment [TME]). The brain TME is made up of tumor cells, and a diverse array of non-cancerous cells, including normal brain cells such as neurons, astrocytes, and microglia. Microglia, the brain's immune cells, play an important role in immune surveillance and defense; and we now understand that microglia help regulate brain metastases. However, little is known about the role of microglia in breast cancer brain metastasis progression, and how the dynamics of "tumor-associated" microglia (TAMs), which reside in the brain tumor, can be modulated for therapeutic benefit.

GOALS
1. Better define the role of tumor-associated microglia (TAMs) in breast-to-brain metastases, including how TAMs communicate with other cells in the microenvironment (i.e., tumor cells, immune cells).

2. Identify a TAM-specific gene profile that correlates with disease progression and patient outcomes. This will help identify subsets of patients whose brain metastases have high levels of unhealthy, or tumor-promoting, TAMs.

3. Evaluate a novel experimental method that targets features of the TME to treat breast cancer brain metastases.

INTERIM OUTCOMES
1. Measure the gene expression profile of TAM cell populations in human patient samples.

2. Identify genes and pathways involved in these TAM functions in order to identify therapeutic targets.

3. Determine whether a cutting-edge experimental method that replaces existing microglia in the mouse brain with new microglia (CDMC transplantation) represents a novel strategy to inhibit or eliminate established brain metastases.

CLINICAL APPLICATIONS/IMPACT
Most research in breast cancer is focused on the biology of the cancer cell. However, we know that cancer cells do not exist in isolation, instead other cell types in the tumor microenvironment can determine whether a metastatic breast cancer cell survives, thrives, or dies. Our proposed study will provide a deeper understanding of TAMs and the ways in which they function to regulate breast-to-brain metastases. It will be the first study of its kind to assess microglia replacement in the context of breast cancer brain metastases. By identifying (**Outcome 1**), targeting (**Outcome 2**), and replacing (**Outcome 3**) TAMs in the tumor microenvironment, we will halt the growth of established brain metastases by targeting "TAM-specific" drivers of immune suppression. We are hopeful that our work will dramatically enhance treatment options for patients with established breast cancer brain metastases.