Public/ Lay Abstract

Poor prognosis, morbidity, and mortality associated with brain metastasis: Greater than 50% of patients with HER2-positive ($HER2^+$) breast cancer develop brain metastasis (BM) during the course of their disease. Brain metastasis is a particularly debilitating form of metastasis that causes cognitive decline, impaired motor function, speech impairment and seizures. Despite progress in understanding its biology, the development of BM becomes fatal for the vast majority of patients with $HER2^+$ breast cancer. The ability to effectively and durably target BM in these patients is therefore likely to significantly improve their survival and quality of life.

Bottlenecks in BM research and treatment: The new generation of brain-penetrant HER2 inhibitors, such as tucatinib, are effective targeted therapies for patients with $HER2^+$ metastatic breast cancer (MBC). Yet, clinical responses are not durable. While most patients respond well initially, cancer cells eventually acquire drug resistance that leads to disease progression and relapse. To effectively eliminate established BM in $HER2^+$ breast cancer, it is important to identify the molecular mediators that fuel the regrowth of BM following HER2-targeted therapy. However, the lack of mouse models of $HER2^+$ MBC that metastasize to the brain has resulted in limited progress in this area. It will be important to determine which biological programs help cancer cells escape targeted therapy and whether they are targetable by drugs. Moreover, biomarkers are needed that can identify patients that are at risk of brain relapse and might benefit from combination treatments. Novel approaches to address these knowledge deficits are expected to transform the MBC treatment landscape.

Our new approach: We recently demonstrated that a protein called "S100A9", that is normally secreted by neutrophils, is aberrantly expressed in EGFR-mutant lung cancer cells that efficiently grow in the brain (Biswas et al., *Cancer Discovery*, 2022). Unlike neutrophils, the cancer cells do not secrete S100A9. Instead, S100A9 functions "within" the cancer cells to activate the ALDH1A1-retinoic acid (RA) pathway, which promotes brain relapse of lung cancer cells both in mouse models and patients. In addition, blocking the S100A9-ALDH1A1-RA axis significantly reduces brain relapse following EGFR-targeted therapy in mouse models, thus revealing the importance of S100A9 as a therapeutic target for BM in EGFR-mutant lung cancer.

To understand the mechanisms of BM in $HER2^+$ MBC, we developed new immunocompetent and xenograft $HER2^+$ allograft mouse models that develop BM and become refractory to anti-HER2 therapies (preliminary studies). Interestingly, we found that S100A9 is also expressed by metastatic $HER2^+$ cancer cells that grow in the brain. Blocking S100A9 in three independent $HER2^{\pm}$ MBC mouse models of BM significantly reduces BM progression. These models either: 1) express ALDH1A1 and might be ALDH1A1-dependent, or 2) do not express ALDH1A1 and may therefore promote BM through ALDH1A1-RA-independent processes. We propose to target S100A9-ALDH1A1-dependent BM using inhibitors of either ALDH1A1 (AT-101) or RA (AGN194310), and to target S100A9-dependent, ALDH1A1-independent BM using a novel S100A9-degrading nanoligase technology. Since $HER2^+$ patient primary breast tumors with S100A9-expressing cancer cells have poor prognoses and shorter survival, we will use diagnostic patient biopsies from metastatic sites to stratify patients with $HER2^+$ MBC who might benefit from S100A9 inactivation or S100A9-pathway inhibition.

Team: This application brings together 4 investigators from Columbia University Medical Center with complementary expertise in cancer biology, drug development, neurobiology, and breast oncology, and the common goal of prolonging survival for MBC patients: Drs. Swarnali Acharyya (mouse models of MBC, S100A9, and BM), Henry Colecraft (nanoligases), Dawn Hershman (clinical translation from preclinical studies), and Peter Canoll (neurobiology and pathology). The team also includes Ms. Joan Mancuso, an experienced patient advocate who was diagnosed with $HER2^+$ MBC, and Dr. Manoj Kandpal (Rockefeller University) for biostatistics.

Innovation: The points of innovation in this application include: (1) A new targetable pathway that can be exploited to treat established BM and prevent new BM progression in $HER2^+$ MBC, based on strong published and preliminary data using novel mouse models of BM, (2) S100A9-nanoligase technology, a novel targeted strategy to directly degrade S100A9 in the body, which will be generated by a pioneer in this field (Dr. Colecraft, co-PI on this proposal), (3) AT-101 and AGN104310 inhibitors are readily available, required in very low doses, and cause no overt toxicities in mice after long-term treatment (our lung cancer studies). Moreover, AT-101 is in Phase 2 clinical trials for other diseases and can be repurposed to BM in MBC (Drs. Hershman and Canoll).

Benefit for diverse populations afflicted with HER2+ MBC: Black women have a 40% higher risk of stage IV $HR^+/HER2^+$ and $HR^-/HER2^+$ breast cancers than White women (PMID 26464428). CUMC treats patients from diverse backgrounds, with a high proportion of Black women. Therefore, our biomarker analysis and novel therapeutic strategies against BM can benefit a large subset of MBCs from diverse backgrounds.