

## **Targeting the unique metabolic profile of brain metastases in breast cancer**

Between 2017 and 2020, the number of women living with stage IV breast cancer in the United States is projected to increase from 155,000 to 170,000. This increase is due in part to improvements in systemic therapies, which allow metastatic breast cancer to be stably managed for long periods of time. However, the onset of brain metastases (BMs) in breast cancer patients is still considered an end-stage event, with no effective drug regimen and median survival after diagnosis measured in months. Moreover, the incidence of BMs is increasing as patients with stage IV breast cancer live longer, since the central nervous system acts as a sanctuary site in which cancer cells are protected from otherwise effective therapies. Thus, there is a pressing need to develop novel treatment strategies for patients with brain-metastatic breast cancer.

In order to fuel their continuous growth, cancer cells must be able to use available nutrient supplies to generate the proteins, lipids, and nucleic acids required for cell proliferation. Metastatic breast cancer cells colonizing the brain encounter a particularly hostile 'nutritional environment', as the levels of many key metabolic fuels such as glucose are much lower than at other sites in the body, in part because they are avidly consumed by neurons. To overcome this challenge, brain-metastatic cancer cells use a metabolic pathway termed oxidative phosphorylation (OXPHOS) to process nutrients as efficiently as possible. Intriguingly, among cancer patients who develop BMs, diabetics being treated with metformin – a weak inhibitor of OXPHOS – have improved outcomes relative to other patient groups. Thus, it is possible that using drugs that suppress OXPHOS could be a novel and effective strategy for treating stage IV breast cancer patients with BMs.

Here, I propose studies designed to evaluate the efficacy of metformin and alternative, more potent, OXPHOS inhibitors in treating breast cancer BMs. I will also test whether drugs targeting other important metabolic processes in BMs can synergize with OXPHOS inhibitors to provide even more effective therapy. Finally, I will use high-throughput approaches to examine how brain-metastatic breast cancer cells adapt to OXPHOS inhibitors, with the intention of identifying possible resistance mechanisms which can be pre-emptively blocked. The overall goal of this proposal is to develop new treatment options for stage IV breast cancer patients with BMs, focusing on drugs that are already approved for other indications in order to streamline potential future clinical application.