Project Title: Targeting eIF4A to Treat TNBC Liver Metastases.

Metastatic triple-negative breast cancer (mTNBC) is one of the most aggressive types of breast cancer. Once it spreads, it is very hard to treat, and the five-year survival rate is only about 12%. Almost half of people with metastatic breast cancer will develop tumors in the liver. When cancer reaches the liver, it is even harder to control. These tumors often resist chemotherapy and create a tumor environment that weakens the body's immune defenses. At the same time, they damage liver function, which harms overall health and can speed up cancer growth. This creates a vicious cycle that shortens survival and reduces quality of life.

Many people with mTNBC must stay on chemotherapy for life to keep the cancer in check. Unfortunately, high doses of chemotherapy cause severe side effects that can make daily life very difficult. There is an urgent need for new treatments that can control liver tumors, protect liver function, help the immune system fight cancer, and reduce treatment toxicity.

Our research focuses on a protein called eIF4A, which plays a key role in how cells make proteins. Cancer cells depend on eIF4A to produce many of the proteins they need to grow, survive, and hide from the immune system. In our recent studies, blocking eIF4A slowed tumor growth in laboratory models of triple-negative breast cancer without causing obvious side effects. Even more importantly, it helped the immune system recognize and attack the cancer. When combined with DNA damaging chemotherapy, blocking eIF4A improved treatment results so much that we could use lower doses of chemotherapy and still control the tumor—reducing harmful side effects.

Early results also suggest that eIF4A may be a key driver of liver metastases. In mouse models of TNBC, blocking eIF4A reduced the number and size of liver tumors, improved liver function, and even reversed harmful cancer-related changes in the blood.

In this project, we will test whether blocking eIF4A—alone or in combination with chemotherapy—can treat established TNBC liver metastases more effectively and with fewer side effects. We will use advanced mouse models that closely mimic how the disease behaves in people. We will also study how blocking eIF4A changes the cancer's protein production and the immune environment in the liver. Using state-of-the-art tools, we aim to find biomarkers that could help identify the patients most likely to benefit from this approach in future clinical trials.

If successful, this research could lead to a treatment strategy that not only controls the cancer, but also preserves liver function, boosts the immune system, and reduces the side effects of lifelong chemotherapy. Because eIF4A-blocking drugs are already in development for other cancers, our findings could quickly move into clinical trials for mTNBC, offering hope for safer, more effective, and more personalized treatment options for people facing this difficult diagnosis.