Lay Abstract: Breast cancer is a common disease that affects millions of people around the world. Currently, treatments often don't cure the disease and can have serious side effects, leading to more health problems and deaths. One important factor in breast cancer is the estrogen receptor alpha (ERα), a protein that can lead to the disease when it doesn't work correctly. Breast cancer cells that are ERα-positive rely on estrogen to grow, making ERα a key target for treatments that block estrogen signals. These treatments, known as endocrine therapies, have been a major breakthrough in cancer treatment over the last 50 years, helping many patients. However, about 20% of patients don't respond to these initial treatments, and up to 50% develop resistance, and the cancer cells resistant to therapy spread and form metastasis for different reasons that are still poorly understood. Understanding why this happens is a big challenge in cancer research.

Initial resistance often arises from a small population of drug-tolerant persister (DTP) cells. Additionally, ERα+ breast cancers are prone to relapse at distant sites, especially in bone, after years or even decades of apparent remission. This phenomenon is attributed to dormant ERα+ tumor cells that can remain in different organs and become reactivated later on. Despite significant survival rates, the long-term outcomes of ER+ breast cancer patients are often compromised by late relapse. Since over 70% of breast cancers are ER-positive and they cause most breast cancer-related deaths, finding new ways to overcome drug resistance and metastasis formation is very important for improving patient survival. The American Cancer Moonshot initiative has identified research on drug resistance as a top priority in cancer research.

Our research proposal aims to uncover how drug-tolerant cells form metastasis after ERα-targeted treatment. We found that calcium signaling, which involves specific proteins that help regulate metastatic cancer cell functions, plays a crucial role in keeping these drug-tolerant cells alive. By blocking this signaling, we could stop these cells from growing and spreading in many organs where they form metastasis. Moreover, we have uncovered a novel function of ERα: in addition to binding DNA, ERα can directly bind RNA, which represents a significant yet overlooked aspect of how ERα helps cancer cells bypass drug treatment. We learned that ERα teams up with a factor known as eIF4A, and this teamwork is crucial for making the proteins that DTP cells use to form metastasis. Because eIF4A is involved in the way these DTP cells help cancer spread, it represents a weak spot—or "Achilles' heel"—that we could target with a clinical inhibitor of eIF4A.

Overall, our research has several key impacts. It improves our understanding of DTP cells and their critical role in helping cancer resist treatment and spread. For many years, we didn't fully understand how these cells function, but this study reveals how they express certain proteins that are essential for their survival. Ultimately, our findings could lead to new treatment options, offering promising new therapies for patients with metastatic breast cancer.