**Public Abstract**

The overarching goal of this study is to identify effective therapeutic strategies to improve the overall survival of patients with metastatic breast cancer, a disease that will claim the lives of 500,000 women across the world every year. The incidence of invasive breast cancer has been increasing since 2004, with more than 2 million cases reported worldwide in 2022. More than 290,000 U.S. cases will be diagnosed in 2022. Fortunately, due to improvements in screening, diagnosis, and treatment, the mortality rate of invasive breast cancer is decreasing in recent years. Treatment differs between the molecular subtypes of breast cancer which are defined by gene expression and clinically approximated by the evaluation of biological markers, primarily the hormone receptors ER (estrogen receptor) and PR (progesterone receptor), as well as the epidermal growth factor receptor HER2. Based on expression of these receptors, breast cancer can be classified into five major molecular subtypes: luminal A, luminal B, HER2-enriched (HER2e), basal-like, and normal-like. In contrast, basal-like breast cancers do not express ER, PR, or HER2, and are therefore referred to as triple-negative breast cancer (TNBC). In ER+ breast cancer, endocrine therapy has proven successful in the treatment of hormone-responsive breast cancer since its early adoption in the 1940s as an ablative therapy. Despite the efficacy of endocrine therapy, resistance arises in about 30% of patients with early-stage disease and in almost all patients who develop metastasis, leading to poor clinical outcome. Overcoming these outcomes is a major challenge in the ER+ breast cancer therapeutic arena. In our efforts to identify new potential therapeutic targets, we discovered that CoREST, a major epigenetic machinery with two enzymatic activities, is a key determinant of resistance to endocrine therapies in breast cancer. Notably, genetic and chemical inhibition of CoREST complex, inhibits proliferation, primary tumor, and metastasis of endocrine resistant breast cancer and TNBC. Additional results revealed a functional interplay between CoREST and the AXL signaling pathway in metastatic breast cancer. The AXL signaling pathway is associated with tumor cell growth, metastasis, invasion, drug resistance, and stem cell maintenance. We hypothesize that dual inhibition of CoREST and the AXL pathway will eradicate metastasis in currently uncurable breast cancers. We will test this hypothesis using xenograft models derived from endocrine resistant models generated in the laboratory, patient-derived tumor organoids and patient-derived xenografts. Also, we will explore the CoREST and the AXL-mediated molecular mechanisms by profiling gene expression changes and CoREST genomic occupancy. Successful completion of this proposal will reveal a novel potential therapeutic option for treating metastatic breast cancer patients.