

## LAY ABSTRACT

For patients with disseminated Estrogen Receptor-positive breast cancer, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, such as palbociclib, have recently emerged as the preferred treatment. Although these drugs, which are used in combination with hormone therapies, are highly effective in these patients, most patients eventually become unresponsive to these treatments. Treatment options for such patients are limited. Furthermore, CDK4/6 inhibitors are ineffective in patients with Triple Negative Breast cancer, who face limited treatment options and high death from this disease.

In this study, we introduce a revolutionary treatment for patients with metastatic, both Estrogen Receptor-positive breast cancer who are unresponsive to CDK4/6 inhibitors. We provide evidence that production of high levels of CDK6 protein in breast tumors renders them unresponsive to CDK4/6 inhibitors. In addition to well-established kinase function (a function that allows transfer of a phosphate group to target proteins) of CDK6, we show that CDK6 also controls turning on and off of genes that are important for growth of breast tumors (by directly binding to regions of genes that control their activity). In this proposal, we will employ highly sophisticated genomic studies to determine how high CDK6 protein levels in breast tumors regulate the activity of genes that promote breast cancer growth and metastasis. We will also employ a highly innovative treatment approach that works by targeting CDK6 (and CDK4) proteins for destruction, thereby eliminating both the kinase function and gene regulation functions (unlike CDK4/6 inhibitors, which only inhibit the kinase function). Supported by preliminary results which show that a drug candidate that causes targeted destruction of CDK6 causes profound growth suppression in tumors that are unresponsive to palbociclib (a CDK4/6 inhibitor), we will validate this treatment strategy in a diverse array of palbociclib-resistant metastatic breast cancer models, including in patient-derived xenograft model.

**Impact:** There are nearly 200,000 women living with disseminated breast cancer in the United States. Over 70% of these women harbor Estrogen Receptor (ER)-positive breast cancer. CDK4/6 inhibitors such as palbociclib, in combination with a hormone therapy, represent the most effective treatment in such patients. However, nearly all Estrogen Receptor-positive breast cancer patients with disseminated disease eventually become unresponsive to these treatments. Treatment options for such patients are severely limited. Successful completion of goals outlined in this proposal will lead to initiation an early phase human clinical trial to evaluate the safety and efficacy of this novel treatment in metastatic, ER+ Breast Cancer patients. Thus, our revolutionary treatment approach has the potential to transform the care of many metastatic ER+ Breast Cancer patients who have become unresponsive to existing treatments.