**Lay Summary**

The recent introduction of cyclin-dependent kinase4/6 (CDK4/6) inhibitors, such as palbociclib, has revolutionized the treatment of metastatic, Estrogen Receptor (ER)-positive breast cancer patients by significantly improving survival when given in combination with a hormone therapy. However, virtually all metastatic breast cancer patients treated with these drugs eventually become unresponsive to them and their cancer will progress. Effective treatment options for such patients are severely limited. Therefore, new treatments that improve survival in metastatic, ER-positive breast cancer patients who have become unresponsive to CDK4/6 inhibitors are urgently needed.

In this study, provide strong evidence that production of high levels of CDK6 protein in ER-positive breast tumors drives unresponsiveness to CDK4/6 inhibitors through both well-established kinase function (a function that allows transfer of a phosphate group to target proteins) and a previously unrecognized non-kinase function. The non-kinase function of CDK6 is not blocked by existing CDK4/6 inhibitors such as palbociclib. Taking advantage of these findings, we develop a new approach for treatment of patients who develop resistance to CDK4/6 inhibitors through high expression of CDK6 that involves eliminating both the kinas and non-kinase functions of the protein. This novel approach may enable effective treatment of patients who have become unresponsive to existing CDK4/6 inhibitors and improve survival of metastatic breast cancer patients.