



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170079

Project Title:
Palbociclib synergizes with autophagy inhibitors to induce senescence in breast cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas M.D. Anderson Cancer Center

Lay Summary:

Newer strategies are needed for the treatment of advanced hormone receptor-positive/HER2-negative breast cancer; the subtype associated with the greatest number of cancer deaths. While agents such as mTOR and CDK 4/6 blockade can delay progression when added to hormonal therapy, no improvement in survival has been observed. Virtually all patients eventually exhibit progression and about one third never respond, or progress within less than 4-6 months. The use of the approved CDK 4/6 inhibitor, palbociclib (PD), also results in neutropenia, necessitating treatment delay or discontinuation. Also, there are no predictive biomarkers to identify tumors with intrinsic and/or acquired resistance to PD. Our preliminary data suggests that inhibition of autophagy could allow lower doses of PD and may augment the overall benefit with little or no added toxicity and at low cost. In addition, the impact of this approach on cell cycle biology could inform additional therapeutic strategies and improve personalization of therapy. Lastly, we have found that several regulators of G1 to S transition are altered in PD resistant cell lines. We propose that PD activates the autophagy pathway to protect ER+ breast cancer cells from PD's activity and that inhibition of autophagy sensitizes cells to PD in vitro and in vivo. We will test this hypothesis by: (i) Clinical testing of autophagy inhibition to enhance the efficacy of low dose PD with hormonal therapy in ER+/HER2- breast cancer patients. (ii) Examine the modulators and downstream effectors of G1/S transition as biomarkers of response to PD. (iii) Examine the preclinical activity of PD and an autophagy inhibitor in treatment of endocrine-resistant tumors in vivo using patient derived xenografts. The successful completion of these clinical and pre-clinical studies will provide the rationale to definitively test this novel combination therapy to overcome endocrine resistance and positively impact survival in patients.