



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120451

Project Title:
Novel Strategy for Treatment of HER2-Positive Breast Cancer

Award Mechanism:
Individual Investigator

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

Lay Summary:

Trastuzumab (Ttzm) is the most effective targeted therapy identified to date for treating patients with metastatic breast cancer. However, resistance to Ttzm is a major obstacle in the clinic. An effective treatment for Ttzm-resistant tumors has not yet been found; thus, many women with metastatic breast cancer will die. To obtain the full benefit of this new drug, we need to understand the mechanisms of drug resistance and develop new therapeutic approaches. JAB1 is a negative regulator of the cell-cycle inhibitor p27. JAB1-overexpressing tumors have a protective barrier against Ttzm-mediated up-regulation of p27. Indeed, JAB1 levels were found to be significantly higher in Ttzm-resistant breast cancer cells than in Ttzm-sensitive breast tumors, suggesting that JAB1 plays a role in resistance mechanisms. Furthermore, inhibiting JAB1 increases the effectiveness of Ttzm treatment by stabilizing p27 levels. This resistance mechanism presents a potential target for therapeutic intervention. Indeed, JAB1 levels are high in aggressive tumors but not in normal tissues and inversely correlate with p27 in breast tumors. Preventing JAB1-p27 interaction results in restabilization of p27 levels and reduces cancer cell growth. JAB1 is a novel candidate oncogene that—when silenced—impressively inhibits breast cancer tumors. Moreover, down-regulation of JAB1 correlates with sensitivity to Ttzm. JAB1 is an important biomarker of Ttzm resistance and is thus an attractive novel therapeutic target; decreasing JAB1 levels or function should be explored as a way to overcome Ttzm resistance in patients with HER2-positive breast cancer. We will investigate the molecular mechanisms by which JAB1 promotes Ttzm resistance and develop a new mouse model to overcome therapeutic resistance and propose innovative therapies to overcome this resistance. Inhibition of JAB1 in combination with Ttzm-targeted therapy to overcome Ttzm resistance would be a groundbreaking achievement.