CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170333

Project Title:
Targeting ubiquitination for cancer therapy

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

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

Lay Summary:

Rationale: The bulk of all deaths from breast cancer are caused by cancer spreading from the breast to distant organs, a process known as metastasis. There are few effective treatments for patients once metastasis occurs. Therefore, there is an urgent unmet need to develop a more effective strategy for targeting metastatic breast cancer. The goal of this study is to develop an innovative therapy to tackle these problems, in particular for triple negative breast cancer (TNBC) patients, by identifying a promising target and developing small molecules to block this target. Our preliminary results and recent studies using genetic approaches have identified a gene named Skp2 as a critical player in breast tumorigenesis and metastasis. Its overexpression is also frequently found in triple negative and human epidermal growth factor receptor 2 (HER2) positive breast cancer, accounting for drug resistance. Using high-throughput computer-aided screening, we identified specific first-in-class Skp2 inhibitors directly binding to Skp2, thus abrogating Skp2 E3 ligase activity toward ubiquitination of p27 and Akt in vitro and in vivo. Remarkably, our Skp2 inhibitors display potent anti-tumor activity in vivo, as a result of Skp2 binding.

Goal: The goal of this proposal is to further optimize our Skp2 inhibitors and test their efficacy in treating metastatic breast cancer. We will move the best candidate forward to preclinical/clinical trials, regulatory approval, product development, and ultimately to bedside for cancer patient treatment. We have proposed three specific aims to accomplish our goals.

Aim 1: To further conduct lead optimization and select superior candidates for preclinical development. Aim 2: To determine the mechanism of action of Skp2 inhibitors and their antitumor and anti-metastasis effects in various TNBC mouse models. Aim 3: To evaluate the efficacy of Skp2 inhibitors in combination cancer therapy and assess their pharmacological and toxicological properties for preclinical development.

The overarching challenge for this proposal is to eliminate the mortality associated with breast cancer, especially TNBC and metastasis. Our study reveals that Skp2 plays a critical role in TNBC tumorigenesis and metastasis, thereby, placing Skp2 in an important position for treating patients with TNBC and metastasis. We have designed novel, potent, selective, and safe Skp2 inhibitors, opening a new avenue of targeting an unconventional protein-protein interaction and signaling pathway. This will lead to the development of promising agents for breast cancer treatment. This synergistic study will translate our

basic findings from laboratory research into the clinical setting efficiently in the near future, and it will have important clinical implications for patients with metastatic TNBC. In addition, our goals will be achieved through a seamless, synergistic collaboration of a multi-institute, multi-disciplinary team, signifying the power of uniting public and private sectors for efficient therapeutics development.