



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
DP150096

Project Title:
ESR1 Coregulator binding site inhibitors (ECBIs) as novel therapeutics to target hormone therapy resistant metastatic breast cancer

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
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Entity:
The University of Texas Health Science Center at San Antonio

Lay Summary:

Endocrine therapies for estrogen receptor (ESR1) positive breast cancer involve modulation of ESR1 signaling using either antiestrogens (AE) or aromatase inhibitors (AI). Despite initial positive response, most patients develop resistance to these drugs and tumors recur as metastases. Resistant tumors retain ESR1-expression, acquire mutations and exhibit alterations in the levels and functions of coregulators that contribute to estrogen independent ESR1-signaling. There is a critical need to develop novel therapeutics that target ligand independent interaction of coregulators with ESR1. AEs/AIs are ineffectual in disrupting ESR1 protein-protein interactions that occur in therapy-resistant and metastatic cells. Towards this end, we have rationally designed a lead small organic molecule (ESR1 coregulator binding inhibitor, ECBI) that can emulate ESR1 coregulator NR box motif in the structural context critical for ESR1 signaling. Our preliminary results show that ECBI can function as natural tumor suppressor, and block tumor growth in vivo. ECBI can control multiple pathways, presenting the prospect of one ECBI blocking numerous protein-protein interactions between critical coregulators with ESR1 in breast cancer, thus has potential to prevent development of resistance to these therapies. ECBI have pharmacologic advantages, associated with fewer systemic side effects and has potential to delay initiation of toxic systemic chemotherapy. Funds from this CPRIT-Bridging the Gap proposal will provide therapeutic utility, biomarker and cGMP-manufactured drug product formulation to enable IND filing and set stage for future initiation of Phase I trials. Successful completion of the proposed studies will lead to the development of first-in-class cancer therapy drugs that addresses the critical need of targeting therapy resistance and metastasis of breast cancer and to commercialize novel drugs that are efficacious against ESR1-coregulator driven breast tumors.