CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170500

Project Title:
Development of next generation steroid receptor coactivator small molecule inhibitors as novel agents to target therapy-resistant breast cancer

Award Mechanism:
Bridging the Gap: Early Translational Research Awards

Principal Investigator:
O'Malley, Bert

Entity:
Baylor College of Medicine

Lay Summary:

Two overarching challenges for current breast cancer treatment are resistance to endocrine therapy in estrogen receptor positive (ER+) breast cancer and tumor metastasis in triple negative breast cancer (TNBC). The objective of this proposal is to develop a novel targeted therapy to address these clinical challenges by inhibiting steroid receptor coactivator 3 (SRC-3) using small molecule inhibitors (SMIs). Our previous work demonstrated that SRC-3 is a master regulator of cellular growth and development which sits at the nexus of many intracellular signaling pathways critical for cancer formation and proliferation. Inhibition of SRC-3 can significantly reduce cancer cell proliferation, motility, and metastasis. In contrast, inhibition of SRC-3 in normal cells does not influence adult mice life span. Due to the many important features of SRC-3, we will explore its potential as a novel target for the development of cancer therapeutics. In a recent study, we identified a highly potent SRC-3 SMI—SI-2. SI-2 can selectively kill breast cancer cells with very high potency and can selectively inhibit SRC-3 protein concentrations while not affecting normal cell viability. Furthermore, in an animal breast tumor model, we showed that SI-2 can significantly inhibit tumor growth and reduce SRC-3 protein levels. In addition, in our toxicology assays, SI-2 does not induce cardiotoxicity or detectable damage to major organs. With this strong preliminary data, we are confident that SI-2 has the potential to be a highly promising drug candidate as an SRC-3 SMI. In this project, we will further optimize SI-2 to search for improved derivatives with favorable pharmacokinetic profiles. We will synthesize and characterize SI-2 SRC-3 SMI ‘unique’ derivatives to identify agents with improved drug-like properties and test the effectiveness of SI-2 derivatives as anti-cancer agents in xenograft animal models of breast cancer. Successful completion of this project will lead to the establishment of a ‘first-in-class’ drug that targets an oncogenic coactivator and will have a significant impact on breast cancer treatment.