



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180844

Project Title:
Regulating Androgen Receptor as a Corepressor by Neurofibromin (NF1)

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Chang, Eric

Entity:
Baylor College of Medicine

Lay Summary:

To treat a given cancer patient with just the right medicine, we must thoroughly understand the molecular factors driving the disease. This project centers on the NF1 gene, the loss of which was first discovered to cause neurofibromatosis type-1, the world's most common hereditary genetic disorder affecting 1 in every 3,000 births. Patients with this disease often develop disfiguring neuronal tissue outgrowth, and have higher propensities for acquiring malignant diseases. We now know that NF1 can also be lost later in life in a wide range of common cancers, such as cancer of the breast, skin, central nervous system, ovaries, etc. Thus, NF1 is a critical tumor suppressor whose normal function is to prevent cancer from developing.

For decades, NF1 was best known as a repressor for Ras proteins, which are among the most potent drivers for cancer when they become constitutively active. As such, NF1-deficient patients are generally treated by drugs targeting the pathways downstream from Ras. But we have discovered a new function of NF1 that is independent of Ras. During the course of studying how estrogen receptor-a positive (ER+) breast cancer overcomes anti-ER treatment, we found that NF1 inactivation de-represses not only Ras but also ER, a major driver of breast cancer. Furthermore, ER is closely related to another nuclear receptor, the androgen receptor (AR). While AR is best known for driving prostate cancer, we have increasing evidence that AR may promote growth and endocrine therapy resistance of breast cancer as well. Thus, in this project, we will investigate whether NF1 directly regulates AR in breast cancer cells, and whether anti-AR agents could therefore have a significant role in suppressing aggressive growth of NF1-deficient breast cancer. Though this project focuses primarily on breast cancer for the present, its success could have a major impact on treatment of prostate cancer and possibly other nuclear receptor driven cancers as well.