CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP150282

Project Title:
Mechanisms of de novo and acquired resistance to therapeutic treatment of bone-metastatic prostate cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
Gallick, Gary

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

Lay Summary:

Many new therapeutics have been approved that prolong the lives of men who have prostate cancer that has metastasized to the bone. However, the effects of these drugs are often short-lived, and tumor cells that are resistant to the therapy regrow, leading to death of the patient. If the mechanisms by which resistance develops were better understood, new drugs or drug combinations may be developed that would delay or prevent therapy resistance. Our studies have focused on mechanisms of resistance with the goal of developing such efficacious drug combinations. An unusual property of prostate cancer bone metastases is that they promote the formation of new bone. In doing so, tumors interacting with this bone lead to release of factors that can then trigger changes in growth-regulatory pathways in tumor cells that increase their survival and thus make them therapy resistant. As these tumor/bone interactions occur even before therapeutic treatment, the resulting resistance they induce is termed “de novo” resistance. This type of resistance due to tumor-bone interaction has not previously been studied prior to our work. We have identified numerous factors released from the bone that we term ”osteocrines” that are known to interact with tumor cells and trigger specific survival pathways. Our goal is to understand how these osteocrines mediate therapy resistance and thus identify combinations of therapies to prolong survival. Unfortunately, tumor cells have many ways of developing resistance, including changes in expression of specific proteins in tumors themselves that render specific therapies ineffective. We have identified a new mechanism of this type of “acquired” resistance, in which a specific signaling molecule becomes overexpressed and compensates for a therapy-targeted molecule. We wish to understand how this mechanism arises and again, use combinations of drugs already in clinical trial to further delay or completely overcome therapy resistance.