CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP160765

Project Title:
An unlikely therapeutic target for malignant bone disease: Dkk-1 activates a stress resistance mechanism in bone tumor cells

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Texas A&M University System Health Science Center

Lay Summary:

About 35% of the 700,000 newly diagnosed cancers in the US will involve serious bone complications. Malignant bone disease (MBD) occurs when tumors initiate in bone or travel to it from other tissues. When they populate bone, tumor cells have a tendency to cause catastrophic damage in the form of osteolytic lesions (OLs). OLs are holes in bone caused by tumors that frequently cause fractures, pain and provide an ideal environment for tumor growth. MBD is typically treated by chemotherapy in an attempt to kill the tumor while bone destruction can be slowed with drugs. Even with these treatments, OLs generally fail to heal, providing an effective environment for tumor survival. The key to effectively treating MBD is to simultaneously target tumor growth and bone destruction while accelerating bone repair. We have discovered that a protein produced by bone tumor cells known as Dickkopf-1 (Dkk-1) has the capacity to inhibit bone repair in surrounding tissues and increase the resistance of tumors to chemotherapy. If we can target Dkk-1 effectively, it may result in a treatment that enhances bone repair in OLs while improving our ability to kill tumor cells, drastically improving our ability to fight MBD. Using a mouse model of bone cancer, we will test 2 approaches for the blockade of Dkk-1 activity. We will test both Dkk-1 blocking strategies in the presence or absence of a common chemotherapeutic, doxorubicin (DRB). If successful, predict that Dkk-1 blockade will increase the effectiveness of DRB when compared to DRB alone. In turn, we expect to observe reduced tumor growth and bone destruction. A successful study will represent the first step in the development of an agent with the combined capacity to preserve bone architecture, stimulate repair of OLs, and increase the effectiveness of chemotherapy during treatment of MBD. Such a drug would be the first of its kind, representing a real opportunity for skeletal recovery and long term remission.