CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180771

Project Title:
Small Molecule for Selective Targeting of Epithelial-Mesenchymal Transition-Induced Cancer Stem Cells

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Taube, Joe

Entity:
Baylor University

Lay Summary:

Nearly half of triple-negative breast cancer (TNBC) patients fail to respond to chemotherapy and suffer median survival rates fewer than 3 years. While hormone- and growth factor receptor-targeted drug treatments have improved outcomes for other subtypes of breast cancer, patients with TNBC face limited options and eventually succumb to either primary tumor recurrence or distant metastases. For TNBC patients with brain metastases median overall survival is less than 5 months.
Tumors are composed of a mixture of distinct cell sub-types which unequally drive progression and response to treatment. Cancer stem cells (CSCs) are often present as a subpopulation of most breast cancers and are responsible for primary tumor recurrence and metastasis to lung, liver and brain. Because of their low proliferation rate and ability to pump many compounds out of the cell, CSCs are frequently resistant to established chemotherapies. In fact, following cessation of chemotherapy, residual tumor material is enriched for CSCs, indicating their resistance to treatment and potential for driving re-emergence of local or distant tumors.

We are looking to natural products which use atypical mechanisms to induce cell death as potential agents targeted to CSCs. We propose to develop a new high-impact treatment for brain-metastatic TNBC patients by pursing a compound which evades CSC-resistance mechanisms and passes through the blood-brain barrier. Our approach is to define the mechanistic pathways which facilitate sensitivity to this compound and chemically-modified derivatives, and to demonstrate utility in a model of brain-metastatic TNBC. This study is high-risk as patients with advanced disease have frequently failed most treatments and are often excluded from clinical trials. Nevertheless, our ultimate goal is to prepare the most successful drug candidate for evaluation in high-impact clinical trials for patients with highly-lethal and treatment-refractory brain-metastatic TNBC.