CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP130485

Project Title:
Targeting Therapy Resistance using Epithelial to Mesenchymal Transition (EMT) Pathways in Preclinical Claudin Low Breast Cancer Models

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Baylor College of Medicine

Lay Summary:

Even with recent advances in cancer therapies many patients still succumb to metastases due to therapeutic resistance and disease recurrence. Recently, solid tumors were found to contain specific subsets of cancer cells that are comparatively more resistant to conventional treatments and which are thought to be responsible for metastasis and recurrence. We have demonstrated that signaling pathways that regulate an embryonic developmental program, known as epithelial-to-mesenchymal transition (EMT), are reactivated in cancers and that these EMT-regulated pathways promote the generation of therapeutically resistant cells. Moreover, these cells exhibit stem cell properties and have gene signatures that overlap with those in treatment-resistant tumor initiating cells(TICs). Therefore, the goal of our proposed studies is to eliminate therapy-resistant cells by specifically targeting the responsible EMT program in tumors. Interestingly, studies from our laboratories have shown that a specific type of breast cancer, termed claudin-low, is especially enriched for TICs and EMT pathways. Indeed, we have generated unique claudin-low tumor models that metastasize to the lung and brain and recapitulate therapy resistance and tumor relapse. Using these models, we previously have identified several microRNAs and signaling molecules that regulate the EMT/MET transition. We will now determine if perturbation of these pathways sensitizes these cells to conventional therapies following expression of one of these microRNAs shown to reverse the EMT phenotype in our claudin-low breast cancer models. In addition, we propose to identify chemical inhibitors of EMT pathways and therapeutic resistance by interrogating libraries of FDA approved drugs. Finally, we will evaluate these new therapeutics either alone or in combination with the “standard of care” chemotherapies in our unique preclinical models.