CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP120489

Project Title:
Transporter-Targeted Drug Delivery and Treatment of Brain Metastases of Breast Cancer

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
Texas Tech University Health Sciences Center

Lay Summary:

Of the >1.3 million people diagnosed with cancer annually in the United States, ~170,000 will eventually develop brain metastases. Brain metastases are extremely difficult tumors to treat with survival rates generally of < 1 year. Chemotherapy shows minimal efficacy, due to the fact that most chemotherapeutic drugs show limited uptake into brain metastases across the brain and tumor vasculature (i.e., blood-brain barrier, BBB). In this proposal, we present exciting preliminary data showing that we have identified a previously unknown drug efflux transporter (Mrp7) at the BBB, which together with one other efflux transporter, may be the primary reason that most breast cancer chemotherapeutic drugs show minimal uptake into brain metastases. We also have identified a drug which can be used in humans to simultaneously inhibit both transporters. When this inhibitor is given in combination with chemotherapy, the amount of breast cancer anticancer drug in brain metastases increases 20-100 fold. This strategy achieves brain metastasis drug concentrations at levels associated with significant tumor kill and regression. This proposal maps out a strategy to translate these findings to establish a new transporter-targeted approach to overcome the BBB. It lays a pathway which may be used as well to overcome the BBB in other cancers with high rates of brain metastases, including lung cancer and melanoma. This application is highly innovative and establishes the role of a major new BBB drug efflux transporter and puts forward inhibitors as well as state-of-the-art brain metastasis model systems to assess the efficacy and safety of this semi-selective approach to open the BBB to key chemotherapeutic drugs. The impact is that it has the strong potential to lead to a major step forward in the successful treatment of brain metastases of breast cancer, which is sorely needed.