



CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140181

Project Title:
Mechanisms of CTC Biomarkers in Breast Cancer Brain Metastasis

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The Methodist Hospital Research Institute

Lay Summary:

Circulating tumor cells (CTCs) are a necessary pre-condition for metastasis to occur. CTCs shed from the primary tumor circulate and survive in the blood, arrest/adhere at distant organ sites, and extravasate at the target organ site to generate metastasis. This proposal is designed to reveal fundamental characteristics of breast cancer brain-colonizing CTCs. We have discovered patient-derived CTCs that possess high competency for breast cancer brain metastasis (BCBM). Importantly, these CTCs go undetected by the current FDA-approved CellSearch™ CTC test that can be “blind” to potentially the most dangerous cancer cells present in the circulation. We have formulated the hypothesis that the CTC signature we have discovered (“Brain Metastasis-Selected Markers” CTC profile), including the important cancer stem cell marker Notch1 and cancer-promoting heparanase (HPSE), is of clinical utility for efficacy of treatment by predicting BCBM; and that Notch1 and heparanase can represent novel therapeutic CTC targets for personalized patient care. Our objective is to test this CTC signature for clinical applicability, thus to validate it in pre-clinical studies directly implicating CTCs isolated from breast cancer patients diagnosed with or without brain metastasis. We will use a novel anti-HPSE inhibitor, called SST0001, which is a non-anticoagulant small molecule which is able to cross the blood-brain barrier. This will be done in conjunction with using non toxic, small-molecule inhibitors of Notch1. We will determine how these two drugs, individually or in synergy (“one-two” punch effect) can affect BCBM by “switching-off” functions of Notch1 and HPSE in brain metastasis-competent CTCs. By the end of projected time, this study can radically help patients at risk of developing BCBM and has the potential for a high payoff. Employing CTCs to improve the prognosis and prediction of BCBM represents a tool of precision medicine to achieve clinical excellence.