

Lay Abstract:

Targeting Tau-induced microtubule stabilization to reduce invasive outgrowth of metastatic tumors

Up to 53% of metastatic breast tumors express a protein called Tau, that is well-known in Alzheimer's disease to stabilize filaments inside cells called microtubules. Microtubule stabilization can promote increased invasion, metastatic dissemination and retention of circulating tumor cells in distant tissues. This proposal will test whether targeting the Tau protein could help stop breast cancer bone metastases from spreading to additional soft tissues (lung, liver, brain) that eventually cause patient death from breast cancer. The most common first site of metastasis is bone, but mortality more often results from the secondary soft tissue metastases. In Aim 1, we will target Tau expression with genetic approaches to provide proof-of-concept that reducing Tau expression could decrease the metastatic behavior of breast tumor cells. In Aim 2, we will test 2 FDA-approved drugs that can decrease Tau expression to see if these drugs also reduce metastatic behaviors and secondary metastasis of breast tumor cells. In Aim 3, we will test an orally-available inhibitor that causes the Tau protein to degrade as another newer way to reduce Tau in a more easily-delivered therapy for patients. Recent data shows that existing chemotherapies can actually cause metastatic dissemination of breast tumors. For Stage 4 patients with bone metastases, this raises the risk that chemotherapy treatment could cause their tumors to spread further to soft tissues that can pose greater hazards for patient survival. This METAvivor project will determine if the Tau protein can be a new target to reduce metastasis and identify therapies that might be used in combination with existing chemotherapies to reduce the risk of metastatic dissemination during treatment. Since we will include 2 FDA-approved anti-Tau therapies for Alzheimer's disease, the results of the current project could more rapidly impact clinical treatment.