Targeting BDNF/TrkB in Brain Metastasis from Young Women with TNBC

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Brain metastasis is a deadly complication for women with breast cancer. In order to prevent and treat this devastating disease, we must understand why and how brain metastases develop and grow. The interaction between metastatic tumor cells and signals occurring at the distant organs are key for growth of metastases, yet we know very little about this interaction, particularly in the brain. Every therapeutic strategy existing today is designed to target cancer cells directly, whether at the primary or metastatic sites. However, we now know that cancer cells change at distant sites in a manner dependent on the new organ environment, and that most therapies work poorly in the brain. *Our studies will test for the first time, if targeting a specific interaction between cancer cells and the brain niche holds value for treatment of established brain metastases*.

The brain is very susceptible to hormones (i.e estradiol) action, as it responds to estradiol produced in the ovaries and in the brain itself. Our studies have shown that this interaction of estradiol with cells in the brain promote growth of brain metastases, even of tumors that do not use estradiol directly to growth. These findings have important implications because being young and premenopausal is a risk factor for development of brain metastasis, and estradiol circulates at high levels in premenopausal women.

Although the tumors that go to the brain usually do not depend on estradiol themselves, we have shown that brain cells secrete different proteins that help cancer cells to grow in the brain when estradiol is around. Astoundingly, if we remove the ovaries and use a drug that impedes the production of estrogen in other organs like the brain itself (called aromatase inhibitor) in mice, we can prevent the formation of brain metastases of a triple negative breast cancer (TNBC) line. We have found that a protein called brain-derived neurotrophic factor (BDNF) is secreted in high amounts when estradiol is around, which “feeds” cancer cells seeded in the brain. Here, we will determine if ovarian ablation alone or in combination with an aromatase inhibitor would have value in treating metastases that have already grown in the brain in a model that mimics young women. Moreover, we will test if we can use ANA-12, a drug that can reach the brain and block BDNF action, to block cancer cells growth in the brain. Therefore, these studies not only fill critical gaps in our knowledge of how cancer cells interact with the brain niche, but could lead to rapid use of FDA-approved aromatase inhibitors to prevent or treat brain metastases.