

Title: Targeting RET for the treatment of breast cancer brain metastasis

Brain metastases occur in 10-15% of patients with metastatic breast cancer and present a major clinical challenge, highlighted by a relatively short survival. Limited therapy options exist for patients with brain metastases and current management consists of surgical resection, radiation therapy and chemotherapy. There is an urgent need to better understand the mechanisms of breast cancer metastasis growth in the brain and to define novel therapeutic targets.

In an effort to understand breast cancer brain metastasis, we directly examined brain metastatic tissue. This is a challenge, as brain metastases are not biopsied and the only available tissue for research is from surgery. We first identified a number of breast cancer cases with metastasis to the brain, and which had received surgical resection, and described the clinical treatments and outcomes in these patients. We then retrieved the surgical specimens from pathology and examined molecular changes compared to the patient's original primary breast cancer. Through this analysis we identified a receptor, RET, which was increased in 38% of the brain metastases. We showed that inhibition of RET blocked growth of human breast cancer brain metastases grown in the laboratory. The protein that activates RET is called Glial cell line-Derived Neurotrophic Factor (GDNF) and is important in survival of neurons in the brain. As such, GDNF is expressed at high levels in the brain and has a critical role in brain development and normal function. **We hypothesize that breast cancers which overexpress RET use GDNF to support their growth and survival in the brain.**

We have developed key preliminary data showing that RET is active in breast cancer cells, is stimulated by GDNF and can be blocked with RET inhibitors. Further, when breast cancer cells overexpress RET they can grow in brain slices in the laboratory far better than breast cancer cells which do not overexpress RET. We thus have the techniques and models to test our hypothesis. Excitingly, there are already FDA-approved therapies against RET. For example, cabometyx (cabozantinib) is approved for treatment of advanced renal cell carcinoma and hepatocellular carcinoma. However, inhibitors such as cabometyx were not developed specifically against RET, they were developed against other targets but have cross reactivity against RET. Importantly, several new drugs specially targeting RET, which have higher specificity and activity, are in clinical development including pralsetinib (BLU-667) and selpercatinib (LOXO-292) which was recently FDA approved in lung and thyroid cancers. We will use these specific inhibitors to test the role of RET in breast cancer growth in cell culture models of the brain microenvironment and develop *in vivo* preclinical data key to testing their ability to block growth of breast cancer brain metastases in patients. These preclinical data will be key to testing if these inhibitors can reduce brain metastases in patients.