## Pleiotrophin as a driver of the immune metastatic niche

***Rationale***: Metastasis of breast cancer cells from a primary tumor to distant organs is responsible for more than 90% of breast cancer deaths. Immune cells, especially macrophages and neutrophils, are critical in conditioning these secondary tumor sites for metastatic seeding and colonization. Our preliminary data suggests that the cytokine Pleiotrophin (**PTN**) augments breast cancer metastasis by increasing the numbers of pro-metastatic macrophages that cluster in metastatic sites. Our preliminary data using a PTN inhibitor (a monoclonal antibody specific for PTN, 3B10) indicate the following:

A. Inhibiting PTN reduces breast cancer metastasis in multiple preclinical models of breast cancer.
B. Inhibiting PTN decreases neutrophil infiltration in the primary tumor and the numbers of macrophage clusters in secondary tumor sites of mice bearing breast tumors.
C. Loss of PTN (by using PTN-deficient mouse models) has the same effect as using a PTN inhibitor.

Therefore, we hypothesize that PTN is expressed by stromal cells in secondary sites and is critical for immune cell promotion of tumor cell colonization and progression in secondary sites.

***Goals***:

**Aim 1. Determine how stromal PTN contributes to immune cell phenotype in metastatic sites.**

- We will investigate differences in the immune cells in metastatic sites of mice treated with 3B10 or a control antibody.
- We will genetically analyze the macrophages that are stimulated by PTN to determine how PTN induces macrophages to promote metastasis.
- We will identify potential PTN receptors and try to understand signaling induced by PTN that might promote metastasis.
- We will confirm our hypothesis that stromal cells are the main source of PTN in breast cancer.

**Aim 2. Determine if PTN inhibition can improve treatment outcomes for patients with metastatic disease.**

- We will determine if PTN inhibition enhances the efficacy of clinically relevant therapy (anti-VEGF, chemotherapy or immune therapy) in mice bearing existing lung metastases.
- Breast cancer patients have elevated levels of plasma PTN, which correlates with lymph node metastasis. However, the clinical impact of PTN expression on breast cancer biology and prognosis is unknown. As a pilot study, PTN levels in plasma from breast cancer patients will be evaluated. We will determine if PTN levels correlate with lymph node metastasis and immune cell recruitment to lymph node metastases.

***Potential Impact***: The short-term translational potential will encompass validation that plasma levels of PTN correlate with metastasis and worse outcome in breast cancer patients. Long-term potential will be investigated by determining if inhibition of PTN is therapeutically meaningful when combined with standard therapy and/or immune therapy. If warranted PTN inhibitors will be pushed towards the clinic.