



Susan G. Komen

Research Grants – Fiscal Year 2015

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Uncovering mechanisms contributing to metastasis and to drug resistance in breast cancer

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Lead Organization: Friedrich Miescher Institute for Biomedical Research

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Public Abstract:

Metastasis is the major cause of breast cancer-related death. If a woman presents with a non-invasive tumor that has not spread to the lymph nodes (LN), she has close to a 100% chance of being alive at 5-years. However, if the tumor has spread to the LNs or is present in distant organs her chances of being alive at 5-years go down to ~ 80% and 25%, respectively. Thus, we need to know more about the process of tumor dissemination and metastasis. Our hypothesis is that by further molecular analyses of breast cancer metastasis we will be able to identify new approaches to prevent this process.

Metastasis is a complex process whereby tumor cells acquire invasive properties and colonize distant sites. Our experimental plan has two aims. In the first aim, we will use models of breast cancer metastasis in the bone in order to test the effect of blocking the well-known Jak/Stat signaling pathway. Using bone metastasis models, in the past three years, our lab has shown that this pathway is consistently active in the bone environment. Jak is a tyrosine kinase and importantly, Jak kinase inhibitors, e.g., Ruxolitinib, are currently being tested in clinical trials. Thus, we hope that by analyzing different bone metastasis models for breast cancer, we will see if blocking this kinase has an impact on tumor growth in the bone.

Our second aim is to block metastatic spread using a novel antibody that targets an extracellular serine protease inhibitor (serpin), called PN-1. My lab showed some years ago, using a metastatic breast cancer



model, that loss (knock-down) of PN-1 leads to a block in the metastatic spread from the primary tumor to the lungs (Fayard et al 2009). In the past few years we showed that the PN-1 blocking antibody (Ab11) prevents PN-1 from binding its receptor, named LRP1. The antibody has been tested in vivo in different metastatic breast cancer models. In all cases we found significantly fewer lung metastases in antibody-treated mice. Using intravital multiphoton imaging directly on the tumors in living animals, we found that Ab11 treatment has a dramatic effect on the tumor environment; we observed a decrease in blood vessel leakiness and a restoration of the collagen matrix surrounding the tumor, both of which could contribute to preventing metastatic spread. Our hypothesis is that by more closely examining the tumor environment from control and Ab11 treated mice we will uncover the mechanism by which metastatic dissemination is blocked.

The research we are proposing to accomplish in the next year will be important for two reasons: first we hope to gain information on the impact of Jak inhibitors on tumor growth in the bone. These inhibitors are now in early stages of clinical development and are being tested in breast cancer patients whose tumors show phosphorylation of Stat3, a transcription factor that is a direct Jak substrate. Second, we hope to uncover the mechanism underlying the anti-metastatic activity of the PN-1 blocking antibody.

