



**Susan G. Komen
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Determining mechanisms of RON kinase signaling in breast cancer metastasis

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Public Abstract:

Breast cancer affects more than 1.3 million women each year and is the leading cause of cancer death in women worldwide. In the US alone, around 40,000 women die of breast cancer each year, largely due to development of metastasis which is mostly resistant to current treatment options. Therefore, there is a clear need for the development of novel therapeutic agents in order to improve the survival rate of these patients, which calls for a deeper understanding of the molecular mechanisms of metastasis. Elevated expression of RON kinase has been reported in various types of human cancers including 50% of primary breast cancer samples. Based on our published results, expression of RON in breast tumors is associated with poor patient prognosis due to development of metastasis. Furthermore, our data show that in addition to RON, a constitutive active isoform known as short-form RON (sfRON) is also concomitantly expressed in some malignant breast tumors and expression of either RON or sfRON render slow growing non-metastatic breast tumors into fast-growing tumors that spontaneously metastasize to different organs. Our intriguing data show that pharmacological RON inhibitors, can significantly inhibit the growth of human primary breast tumor grafts with high RON expression, although it is not known which signaling pathway is responsible for RON-induced metastasis. We have shown that the molecular mechanism through which sfRON contributes to tumor progression and metastasis lies in activation of PI3K pathway and that combination treatment of these tumors with RON and PI3K inhibitors is more effective than RON inhibition alone. The goal of this proposal is to unravel molecular mechanisms behind RON signaling responsible for metastasis induction, so that novel treatment strategies can be designed based on efficient targeting of RON and relevant downstream effectors. We expect that combination therapy should decrease the chance of resistance to single anticancer agents and therefore should have better efficacy in prolonging breast cancer patients' survival. In addition, we have also determined that some breast tumors co-express both RON and sfRON. However, the functional consequences of expression of both isoforms in terms of tumor progression and metastasis has not been clarified. This information will provide clinical insight as to whether different single or combination targeted therapies based on RON/sfRON and specific relevant downstream signaling should be considered when breast cancer patients are positive for single or both isoforms. We believe that fulfillment of the aims in this proposal will provide mechanistic insight about RON's contribution to metastasis, the results of which can be exploited in designing the most effective future clinical trials aimed toward increased survival of breast cancer patients in the short term.